

been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1192 (shown in Figure 280 and SEQ ID NO:389) has amino acid sequence identity with trout PO-like glycoprotein (GEN12838 IP1). Accordingly, it is presently believed that PRO1192 disclosed in the present application is a newly identified member of the myelin P0 glycoprotein family.

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123. Full-length PRO1160 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1160. In particular, cDNA encoding a PRO1160 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

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The DNA62872-1509 clone was isolated from a human breast tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA62872-1509 clone does encode a secreted factor. As far as is known, the DNA62872-1509 sequence encodes a novel factor designated herein as PRO1160; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

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124. Full-length PRO1187 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1187. In particular, cDNA encoding a PRO1187 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

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As far as is known, the DNA62876-1517 sequence encodes a novel factor designated herein as PRO1187; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed.

125. Full-length PRO1185 Polypeptides

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1185. In particular, cDNA encoding a PRO1185 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA62881-1515 clone encodes a novel factor designated herein as PRO1185; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed.

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126. Full-length PRO1345 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1345. In particular, cDNA encoding a PRO1345 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

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Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1345 (shown in Figure 288 and SEQ ID NO:403) has amino acid sequence identity with

the C-type lectin homolog precursor protein of bos taurus (BTU22298_1). Accordingly, it is presently believed that PRO1345 disclosed in the present application is a newly identified member of the C-type lectin protein family and may possess activity typical of that family or of the tetranectin protein in particular.

127. Full-length PRO1245 Polypeptides

5 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1245. In particular, cDNA encoding a PRO1245 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

 The DNA64884-1527 clone was identified using methods that selects for nucleotide sequences encoding secreted proteins. As far as is known, the DNA64884-1527 sequence encodes a novel secreted factor designated
10 herein as PRO1245. Using WU-BLAST2 sequence alignment computer programs, some sequence identities to known proteins were revealed; however, it was determined that they were not significant.

128. Full-length PRO1358 Polypeptides

 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides
15 referred to in the present application as PRO1358. In particular, cDNA encoding a PRO1358 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

 Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1358 (shown in Figure 292 and SEQ ID NO:410) has amino acid sequence identity with RASP-1. Accordingly, it is presently believed that PRO1358 disclosed in the present application is a newly identified
20 member of the serpin family of serine protease inhibitors and may possess serine protease inhibition activity, protein catabolism inhibitory activity and/or be associated with regeneration of tissue.

129. Full-length PRO1195 Polypeptides

 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides
25 referred to in the present application as PRO1195. In particular, cDNA encoding a PRO1195 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

 Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1195 (shown in Figure 294 and SEQ ID NO:412) has amino acid sequence identity with MMU28486_1, termed a proline rich acidic protein from Mus musculus, locus MMU28486, Accession:
30 U28486, database GBTRANS, submitted 06-JUN-1995 by John W. Kasik. Accordingly, it is presently believed that PRO1195 disclosed in the present application is a newly identified member of this protein family.

130. Full-length PRO1270 Polypeptides

 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides
35 referred to in the present application as PRO1270. In particular, cDNA encoding a PRO1270 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1270 (shown in Figure 296 and SEQ ID NO:414) has amino acid sequence identity with the lectin protein (XLU86699_1) of *Xenopus laevis*. Accordingly, it is presently believed that PRO1270 disclosed in the present application is a newly identified member of the lectin protein family and may possess activity typical of that family.

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131. Full-length PRO1271 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1271. In particular, cDNA encoding a PRO1271 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

10 As far as is known, the DNA66309-1538 sequence encodes a novel factor designated herein as PRO1271; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed (results further described in the examples below).

132. Full-length PRO1375 Polypeptides

15 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1375. In particular, cDNA encoding a PRO1375 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1375 (shown in Figure 300 and SEQ ID NO:418) has amino acid sequence identity PUT2. Accordingly, it is presently believed that PRO1375 disclosed in the present application has at least one related mechanism of PUT2.

133. Full-length PRO1385 Polypeptides

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1385. In particular, cDNA encoding a PRO1385 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA68869-1610 clone was isolated from a human tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA68869-1610 clone does encode a secreted factor. As far as is known, the DNA68869-1610 sequence encodes a novel factor designated herein as PRO1385; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

134. Full-length PRO1387 Polypeptides

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1387. In particular, cDNA encoding a PRO1387 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1387 (shown in Figure 304 and SEQ ID NO:422) has amino acid sequence identity with the myelin p0 protein precursor (MYPO_HETFR). Accordingly, it is presently believed that PRO1387 disclosed in the present application is a newly identified member of the myelin protein family and may possess activity typical of that family.

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135. Full-length PRO1384 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1384. In particular, cDNA encoding a PRO1384 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

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Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1384 (shown in Figure 306 and SEQ ID NO:424) has amino acid sequence identity with NKG2-D (AF054819_1; Dayhoff database, version 35.45 SwissProt 35). Accordingly, it is presently believed that PRO1384 disclosed in the present application is a newly identified member of the NKG2 family and may possess MHC activation/inactivation activities typical of the NKG2 family.

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B. PRO Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

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Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

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PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein.

Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

- PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 1 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 1, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 1

	<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
10	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe;	
15		norleucine	leu
	Leu (L)	norleucine; ile; val;	
		met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
20	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
25	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe;	
		ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- 35 (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

40 Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant

DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

10 C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

20 Other modifications include deamidation of glutamyl and asparaginy residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

25 Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

30 Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., *supra*; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., *supra*.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., *supra*, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA* ; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7*

ilvG kar^r; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning
 5 or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 737 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC
 10 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g.,
 15 *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotrophic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*,
 20 *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells.
 25 More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT
 30 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector
 35 may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally

include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

5 The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g.,
10 the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral
15 secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for
20 cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

25 An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature,
30 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well
35 known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid

promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

5 Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

10 Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

15 PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

20 Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 25 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

30 Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., 35 Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

E. Uses for PRO

Nucleotide sequences (or their complement) encoding PRO have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.

The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ³²P or ³⁵S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO_4 -mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral
5 vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable
10 ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target
15 nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO coding sequences.

Nucleotide sequences encoding a PRO can also be used to construct hybridization probes for mapping
20 the gene which encodes that PRO and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO encode a protein which binds to another protein (example, where
25 the PRO is a receptor), the PRO can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO or
30 a receptor for PRO. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

35 Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene,

which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a PRO "knock out" animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the PRO polypeptide.

Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA.

Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau *et al.*, Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem. 262, 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson *et al.*, Science 256, 808-813 (1992).

The PRO polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes.

The nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO polypeptides and nucleic acid molecules of the present invention may also be used for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another. PRO nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the

dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, PLURONICS™ or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In *Toxicokinetics and New Drug Development*, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 µg/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- (rhIFN-), interleukin-2, and MN rgp120. Johnson et al., Nat. Med., 2:795-799 (1996); Yasuda, Biomed. Ther., 27:1221-1223 (1993); Hora et al., Bio/Technology, 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine Design: The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many

transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a

single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiationsite, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

5 Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

10 These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

PRO189 can be used in assays with W01A6.1 of *C. Elegans*, phosphodiesterases, transporters and proteins which bind to fatty acids, to determine the relative activities of PRO189 against these proteins. The results can be applied accordingly.

15

F. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

20

1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

25

30 The immunization protocol may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975).

35 In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103].

- 5 Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will
- 10 include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

- Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk
- 15 Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

- The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of
- 20 monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

- 25 After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

- The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture
- 30 medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

- The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding
- 35 specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells,

or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., *supra*] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers

[Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks et al., Bio/Technology 10, 779-783 (1992); Lonberg et al., Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild et al., Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in

at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with

the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

- 5 Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize
- 10 cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

15 5. Heteroconjugate Antibodies

- Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro*
- 20 using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

25 6. Effector Function Engineering

- It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased
- 30 complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-
- 35 Cancer Drug Design, 3: 219-230 (1989).

7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above.

- 5 Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are
10 available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

- Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-
15 diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

- 20 In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

25 8. Immunoliposomes

- The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No.
30 5,013,556.

- Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin
35 *et al.*, J. Biol. Chem., **257**: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, J. National Cancer Inst., **81**(19): 1484 (1989).

9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide-interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

G. Uses for anti-PRO Antibodies

The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, *e.g.*, detecting its expression in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases

5 [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or

10 horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture

15 or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the

20 antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

25

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas,

30 VA.

EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about

35 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (*e.g.*, Dayhoff, GenBank), and proprietary databases (*e.g.* LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program WU-BLAST-2

(Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

5 Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of WU-BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

EXAMPLE 2: Isolation of cDNA clones by Amylase Screening

25 1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linked cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

2. Preparation of random primed cDNA library

35 A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA

was sized to 500-1000 bp, linked with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately

5 transfected yeast colonies.

3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then
10 electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

15 The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL⁺, SUC⁺, GAL⁺. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*, *sec62*, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p)
25 or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et al., Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., Methods in Yeast Genetics,
30 Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2×10^6 cells/ml (approx. OD₆₀₀=0.1) into fresh YEPD broth (500 ml) and regrown to 1×10^7 cells/ml (approx. OD₆₀₀=0.4-0.5).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water,
35 and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li₂OOCCH₃), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 μ l) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 μ g, vol. < 10 μ l) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 μ l, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li₂OOCCH₃, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 μ l, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 μ l) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 μ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 μ l) was used as a template for the PCR reaction in a 25 μ l volume containing: 0.5 μ l Klentaq (Clontech, Palo Alto, CA); 4.0 μ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 μ l Kentaq buffer (Clontech); 0.25 μ l forward oligo 1; 0.25 μ l reverse oligo 2; 12.5 μ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACGACGCGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:3)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAATCCATT-3' (SEQ ID NO:4)

PCR was then performed as follows:

- a. Denature 92°C, 5 minutes
- b. 3 cycles of: Denature 92°C, 30 seconds

		Anneal	59°C, 30 seconds
		Extend	72°C, 60 seconds
5	c.	3 cycles of:	
		Denature	92°C, 30 seconds
		Anneal	57°C, 30 seconds
		Extend	72°C, 60 seconds
10	d.	25 cycles of:	
		Denature	92°C, 30 seconds
		Anneal	55°C, 30 seconds
		Extend	72°C, 60 seconds
	e.	Hold	4°C

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present.

15 Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 µl) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., supra.

20 Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO281

In order to obtain a cDNA clone encoding PRO281, methods described in Klein et al., Proc. Natl. Acad. Sci. USA 93:7108-7113 (1996) were employed with the following modifications. Yeast transformation was performed with limiting amounts of transforming DNA in order to reduce the number of multiple transformed yeast cells. Instead of plasmid isolation from the yeast followed by transformation of *E. coli* as

described in Klein et al., supra, PCR analysis was performed on single yeast colonies. PCR primers employed were bipartite in order to amplify the insert and a small portion of the invertase gene (allowing to determine that the insert was in frame with invertase) and to add on universal sequencing primer sites.

An invertase library was transformed into yeast and positives were selected on sucrose plates. Positive clones were re-tested and PCR products were sequenced. The sequence of one clone, PRO281, was determined to contain a signal peptide coding sequence. Oligonucleotide primers and probes were designed using the nucleotide sequence of PRO281. A full length plasmid library of cDNAs from human umbilical vein endothelium tissue was titered and approximately 100,000 cfu were plated in 192 pools of 500 cfu/pool into 96-well round bottom plates. The plates were sealed and pools were grown overnight at 37°C with shaking (200rpm). PCR was performed on the individual cultures using primers. Agarose gel electrophoresis was performed and positive wells were identified by visualization of a band of the expected size. Individual positive clones were obtained by colony lift followed by hybridization with ³²P-labeled oligonucleotide. These clones were characterized by PCR, restriction digest, and southern blot analyses.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 80-82, and a stop signal at nucleotide positions 1115-1117 (Figure 1, SEQ ID NO:1). The predicted polypeptide precursor is 345 amino acids long, has a calculated molecular weight of approximately 37,205 daltons and an estimated pI of approximately 10.15. Analysis of the full-length PRO281 sequence shown in Figure 2 (SEQ ID NO:2) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 14, multiple transmembrane domains from about amino acid position 83 to about amino acid position 105, from about amino acid position 126 to about amino acid position 146, from about amino acid position 158 to about amino acid position 177, from about amino acid position 197 to about amino acid position 216, from about amino acid position 218 to about amino acid position 238, from about amino acid position 245 to about amino acid position 265, and from about amino acid position 271 to about amino acid position 290 and an amino acid sequence block having homology to G-protein coupled receptor proteins from about amino acid 115 to about amino acid 155. Clone UNQ244 (DNA16422-1209) has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209929.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 2 (SEQ ID NO:2), evidenced significant homology between the PRO281 amino acid sequence and the following Dayhoff sequences: H64634, AF033095_1, B64815, YBHL_ECOLI, EMEQUTR_1, AF064763_3, S53708, A69253, AF035413_12 and S63281.

EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO276

In order to obtain a cDNA clone encoding PRO276, methods described in Klein et al., PNAS, 93:7108-7113 (1996) were employed with the following modifications. Yeast transformation was performed with limiting amounts of transforming DNA in order to reduce the number of multiple transformed yeast cells. Instead of plasmid isolation from the yeast followed by transformation of *E. coli* as described in Klein et al., supra, PCR analysis was performed on single yeast colonies. PCR primers employed were bipartite in order to amplify the

insert and a small portion of the invertase gene (allowing to determine that the insert was in frame with invertase) and to add on universal sequencing primer sites.

An invertase library was transformed into yeast and positives were selected on sucrose plates. Positive clones were re-tested and PCR products were sequenced. The sequence of one clone, PRO276, was determined to contain a signal peptide coding sequence. Oligonucleotide primers and probes were designed using the nucleotide sequence of PRO276. A full length plasmid library of cDNAs from human fetal liver cells was titrated and approximately 100,000 cfu were plated in 192 pools of 500 cfu/pool into 96-well round bottom plates. The plates were sealed and pools were grown overnight at 37 C with shaking (200rpm). PCR was performed on the individual cultures using primers. Agarose gel electrophoresis was performed and positive wells were identified by visualization of a band of the expected size. Individual positive clones were obtained by colony lift followed by hybridization with ³²P-labeled oligonucleotide. These clones were characterized by PCR, restriction digest, and southern blot analyses.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 180-182 and a stop signal at nucleotide positions 933-935 (Figure 3; SEQ ID NO:5). The predicted polypeptide precursor is 251 amino acids long has a calculated molecular weight of approximately 28,801 daltons and an estimated pI of approximately 9.58. The transmembrane domains are approximately at amino acids 98-116 and 152-172 of the sequence shown in Figure 4 (SEQ ID NO:6). Clone DNA16435-1208 (UNQ243) has been deposited with the ATCC and is assigned ATCC deposit no. 209930.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 4 (SEQ ID NO:6), revealed some sequence identity between the PRO276 amino acid sequence and the following Dayhoff sequences: CEG25D7_2, ATT8O5_2, S69696, GRHR_RAT, NPCBAABCD_3, AB013149_1, P_R85942 and AP000006_5.

EXAMPLE 6: Isolation of cDNA clones Encoding Human PRO189

A clone designated herein as DNA14187 was isolated as described in Example 2 above from a human retina tissue library. The DNA14187 sequence is shown in Figure 7 (SEQ ID NO:9). Based on the DNA14187 sequence shown in Figure 7 (SEQ ID NO:9), oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO189. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TTGACCTATACAGAGATTCATC-3' (SEQ ID NO:10); and
reverse PCR primer 5'-CTAAGAACTTCCTCAGGATTTT-3' (SEQ ID NO:11).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA14187 sequence which had the following nucleotide sequence:

hybridization probe

5'-ATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGC-3' (SEQ ID NO:12).

5 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO189 gene using the probe oligonucleotide and one of the PCR primers.

10 RNA for construction of the cDNA libraries was isolated from human retina tissue (LIB94). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

15 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO189 and the derived protein sequence for PRO189.

The entire nucleotide sequence of DNA21624-1391 is shown in Figure 5 (SEQ ID NO:7). Clone DNA21624-1391 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 200-202 and ending at the stop codon at nucleotide positions 1301-1303 (Figure 5). The predicted polypeptide precursor is 367 amino acids long (Figure 6). The full-length PRO189 protein shown in Figure 6
20 has an estimated molecular weight of about 41,871 daltons and a pI of about 5.06. Clone DNA21624-1391 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analyzing the amino acid sequence of SEQ ID NO:8, the putative N-glycosylation sites are at about amino acids 224-227, 246-249 and 285-288. A domain for cytosolic fatty-acid binding proteins is at amino acids
25 78-107 of SEQ ID NO:8. The corresponding nucleotides can be routinely determined given the sequences provided herein.

Some sequence identity was found to W01A6.1 and F35D11.11, *C. Elegans* proteins, designated in a Dayhoff database as CEW01A6_10 and CELF35D11_11, respectively. Some sequence identity was also found to an antigen to malaria and to restin, designated in a Dayhoff database as P_R05766 and AF014012_1,
30 respectively. Some sequence identity was also found to a microtubule binding protein and to myosin, designated in a Dayhoff database as AF041382_1 and S07537, respectively. There is also some sequence identity with 1-phosphatidylinositol-4, 5-bisphosphate, designated as PIP1_RAT.

EXAMPLE 7: Isolation of cDNA clones Encoding Human PRO190

35 A clone designated herein as DNA14232 was isolated as described in Example 2 above from a human fetal retina tissue library. The DNA14232 sequence is shown in Figure 10 (SEQ ID NO:15). Based on the DNA14232 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained

the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO190. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTATACCTACTGTAGCTTCT-3' (SEQ ID NO:16); and

reverse PCR primer 5'-TCAGAGAATTCCTTCCAGGA-3' (SEQ ID NO:17).

- 10 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA14232 sequence which had the following nucleotide sequence:

hybridization probe

5'-ACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCACAA-3' (SEQ ID NO:18).

- 15 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO190 gene using the probe oligonucleotide and one of the PCR primers.

- RNA for construction of the cDNA libraries was isolated from human retina tissue (LIB94). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

- 25 DNA sequencing of the clones isolated as described above gave sequences which include the full-length DNA sequence for PRO190 [herein designated as DNA23334-1392] (SEQ ID NO:13) and the derived protein sequence for PRO190.

- The entire nucleotide sequence of DNA23334-1392 is shown in Figure 8 (SEQ ID NO:13). Clone DNA23334-1392 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 193-195 and which ends at the stop codon at nucleotide positions 1465-1467 (Figure 8). The predicted polypeptide precursor is 424 amino acids long (Figure 9). The full-length PRO190 protein shown in Figure 9 has an estimated molecular weight of about 48,500 daltons and a pI of about 8.65. Clone DNA23334-1392 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

- 35 Analyzing the amino acid sequence of SEQ ID NO:14, the putative transmembrane domains are at about amino acids 16-36, 50-74, 147-168, 229-250, 271-293, 298-318 and 328-368 of SEQ ID NO:14. N-glycosylation sites are at about amino acids 128-131, 204-207, 218-221 and 274-377 of SEQ ID NO:14. The corresponding nucleotides can be routinely determined given the sequences provided herein.

PRO190 has sequence identity with at least the following Dayhoff sequences designated as: CEZK896_2, JC5023, GMS1_SCHPO and S44668.

EXAMPLE 8: Isolation of cDNA clones Encoding Human PRO341

A clone designated herein as DNA12920 was isolated as described in Example 2 above from a human placenta tissue library. The DNA12920 sequence is shown in Figure 13 (SEQ ID NO:21). The DNA12920 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA25314. Oligonucleotide primers based upon the DNA25314 sequence were then synthesized and employed to screen a human placenta cDNA library which resulted in the identification of the DNA26288-1239 clone shown in Figure 11. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 380-382, and a stop signal at nucleotide positions 1754-1756 (Figure 11, SEQ ID NO:19). The predicted polypeptide precursor is 458 amino acids long, has a calculated molecular weight of approximately 50,264 daltons and an estimated pI of approximately 8.17. Analysis of the full-length PRO341 sequence shown in Figure 12 (SEQ ID NO:20) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 17, transmembrane domains from about amino acid 171 to about amino acid 190, from about amino acid 220 to about amino acid 239, from about amino acid 259 to about amino acid 275, from about amino acid 286 to about amino acid 305, from about amino acid 316 to about amino acid 335, from about amino acid 353 to about amino acid 378 and from about amino acid 396 to about amino acid 417 and potential N-glycosylation sites from about amino acid 145 to about amino acid 147 and from about amino acid 155 to about amino acid 158. Clone DNA26288-1239 has been deposited with ATCC on April 21, 1998 and is assigned ATCC deposit no. 209792.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 12 (SEQ ID NO:20), evidenced homology between the PRO341 amino acid sequence and the following Dayhoff sequences: S75696, H69788, D69852, A69888, B64918, F64752, LPU89276_1, G64962, S52977 and S44253.

EXAMPLE 9: Isolation of cDNA clones Encoding Human PRO180

A clone designated herein as DNA12922 was isolated as described in Example 2 above from a human placenta tissue library. The DNA12922 sequence is shown in Figure 16 (SEQ ID NO:24). The DNA12922 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a

proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

5 An oligonucleotide probe was formed based upon the consensus sequence obtained above. This probe had the following sequence.

5'-ACCTGTTAGAAATGTGGTGGTTTCAGCAAGGCCTCAGTTT (SEQ ID NO:25).

This probe was used to screen a human placenta library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, 10 Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp. A clone designated herein as DNA26843-1389 was obtained.

The entire nucleotide sequence of DNA26843-1389 is shown in Figure 14 (SEQ ID NO:22). Clone DNA26843-1389 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and ending at the stop codon at nucleotide positions 919-921 (Figure 14). The predicted 15 polypeptide precursor is 266 amino acids long (Figure 15). The full-length PRO180 protein shown in Figure 15 has an estimated molecular weight of about 29,766 daltons and a pI of about 8.39. Clone DNA26843-1389 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Still analyzing the amino acid sequence of SEQ ID NO:23, the transmembrane domains are at about 20 amino acids 13-33 (type II), 54-73, 94-113, 160-180 and 122-141 of SEQ ID NO:23. N-myristoylation sites are at about amino acids 57-62, 95-100, 99-104, 124-129 and 183-188 of SEQ ID NO:23. The corresponding nucleotides can be routinely determined given the sequences provided herein.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 15 (SEQ ID NO:23), evidenced some sequence 25 identity between the PRO180 amino acid sequence and the following Dayhoff sequences: CEC33A11_2, CEG11E6_5, CELW03A5_1 AND PEU83861_2 (NADH dehydrogenase subunit 4L, mitochondrion).

EXAMPLE 10: Isolation of cDNA clones Encoding Human PRO194

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described 30 in Example 1 above. This consensus sequence is herein DNA19464. Based on the DNA19464 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO194. PCR primers (forward and reverse) were synthesized based upon the DNA19464 sequence. Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA19464 sequence.

35 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO194 gene using the probe oligonucleotide and one of the PCR primers. RNA

for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO194 [herein designated as DNA26844-1394] (SEQ ID NO:27) and the derived protein sequence for PRO194.

5 The entire nucleotide sequence of DNA26844-1394 is shown in Figure 17 (SEQ ID NO:27). Clone DNA26844-1394 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 81-83 and ending at the stop codon at nucleotide positions 873-875 (Figure 17). The predicted polypeptide precursor is 264 amino acids long (Figure 18). The full-length PRO194 protein shown in Figure 18 has an estimated molecular weight of about 29,665 daltons and a pI of about 9.34. Analysis of the full-length PRO194 sequence shown in Figure 18 (SEQ ID NO:28) evidences the presence of various important polypeptides domains as shown in Figure 18. Clone DNA26844-1394 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209926.

Analysis of the amino acid sequence of the full-length PRO194 polypeptide suggests that it does not exhibit significant sequence similarity to any known human protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some homology between the PRO194 amino acid sequence and the following Dayhoff sequences, HUMORFT_1, CET07F10_5, ATFCA9_12, F64934, YDJX_ECOLI, ATAF00065719F29G20.19, H70002, S76980, H64934 and S76385.

EXAMPLE 11: Isolation of cDNA clones Encoding Human PRO203

20 A clone designated herein as DNA15618 was isolated as described in Example 2 above from a human fetal lung tissue library. The DNA15618 sequence is shown in Figure 21 (SEQ ID NO:31). Oligonucleotide probes were generated from the sequence of the DNA15618 molecule and were used to screen a human fetal lung library (LIB26) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

25 A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 159-161 and ending at the stop codon found at nucleotide positions 1200-1202 (Figure 19; SEQ ID NO:29). The predicted polypeptide precursor is 347 amino acids long, has a calculated molecular weight of approximately 39,870 daltons and an estimated pI of approximately 6.76. Analysis of the full-length PRO203 sequence shown in Figure 20 (SEQ ID NO:30) evidences the presence of the following: a type II transmembrane domain at about amino acid 64 to about amino acid 87; possible N-glycosylation sites at about amino acid 147 to about amino acid 150, about amino acid 155 to about amino acid 158, and about amino acid 237 to about amino acid 240; sequence identity with heavy-metal-associated domain proteins at about amino acid 23 to about amino acid 45, and sequence identity with D-isomer specific 2-hydroxyacid dehydrogenase at about amino acid 24 to about amino acid 34. Clone DNA30862-1396 was 30 deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209920.

Analysis of the amino acid sequence of the full-length PRO203 polypeptide suggests that it possesses sequence similarity to GST ATPase, thereby indicating that PRO203 may be a novel GST ATPase. More

specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO203 amino acid sequence and the following Dayhoff sequences, AF008124_1, CFRCD1GEN_1, and P_R82566.

EXAMPLE 12: Isolation of cDNA clones Encoding Human PRO290

5 An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified that had homology to beige and FAN. An oligonucleotide probe based upon the identified EST sequence was then synthesized and used to screen human fetal kidney cDNA libraries in an attempt to identify a full-length cDNA clone. The oligonucleotide probe had the following sequence:

5' TGACTGCACTACCCCGTGGCAAGCTGTTGAGCCAGCTCAGCTG 3' (SEQ ID NO:34).

10 RNA for construction of cDNA libraries was isolated from human fetal kidney tissue. The cDNA libraries used to isolate the cDNA clones encoding human PRO290 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science 253:1278-1280 (1991)) in the unique XhoI and NotI.

15 A cDNA clone was identified and sequenced in entirety. The entire nucleotide sequence of DNA35680-1212 is shown in Figure 22 (SEQ ID NO:32). Clone DNA35680-1212 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 293-295, and a stop codon at nucleotide positions 3302-3304 (Figure 22; SEQ ID NO:32). The predicted polypeptide precursor is 1003 amino acids long.

20 It is currently believed that the PRO290 polypeptide is related to FAN and/or beige. Clone DNA35680-1212 has been deposited with ATCC and is assigned ATCC deposit no. 209790. It is understood that the deposited clone has the actual correct sequence rather than the representations provided herein. The full-length PRO290 protein shown in Figure 23 has an estimated molecular weight of about 112,013 daltons and a pI of about 6.4.

EXAMPLE 13: Isolation of cDNA Clones Encoding Human PRO874

25 A consensus DNA sequence designated herein as DNA36459 was identified using phrap as described in Example 1 above. Based on the DNA36459 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the coding sequence for PRO874.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TCGTGCCCAGGGGCTGATGTGC-3' (SEQ ID NO:37); and

reverse PCR primer 5'-GTCTTTACCCAGCCCCGGGATGCG-3' (SEQ ID NO:38).

35 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36459 sequence which had the following nucleotide sequence:

hybridization probe

5'-GGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCCTGGG-3' (SEQ ID NO:39).

In order to screen several libraries for a source of a clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO874 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the DNA sequence for PRO874 [herein designated as DNA40621-1440] (SEQ ID NO:35) and the derived protein sequence for PRO874.

The entire nucleotide sequence of DNA40621-1440 is shown in Figure 24 (SEQ ID NO:35). Clone DNA40621-1440 contains a single open reading frame ending at the stop codon at nucleotide positions 964-966 (Figure 24). The predicted polypeptide encoded by DNA40621-1440 is 321 amino acids long (Figure 25). The PRO874 protein shown in Figure 25 has an estimated molecular weight of about 36,194 daltons and a pI of about 9.85. Analysis of the PRO874 sequence shown in Figure 25 (SEQ ID NO:36) evidenced the presence of the following: a type II transmembrane domain at about amino acids 57-80; additional transmembrane domains at about amino acids 110-126, 215-231, and 254-274; potential N-glycosylation sites at about amino acids 16-19, 27-30, and 289-292; sequence identity with hypothetical YBR002c family proteins at about amino acids 276-287; and sequence identity with ammonium transporter proteins at about amino acids 204-230. Clone DNA40621-1440 was deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209922.

Analysis of the amino acid sequence of the PRO874 polypeptide suggests that it is a novel multi-span transmembrane protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO874 amino acid sequence and the following Dayhoff sequences: S67049, AF054839_1, S73437, S52460, and HIVU80570_1.

EXAMPLE 14: Isolation of cDNA Clones Encoding Human PRO710

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins.

Use of this yeast screening assay allowed identification of a single cDNA clone whose sequence (herein designated as DNA38190) is shown in Figure 28 (SEQ ID NO:42). Based on the DNA38190 sequence shown in Figure 28, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO710. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TTCCGCAAAGAGTTCTACGAGGTGG-3' (SEQ ID NO:43)

reverse PCR primer 5'-ATTGACAACATTGACTGGCCTATGGG-3' (SEQ ID NO:44)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA38190 sequence which had the following nucleotide sequence

hybridization probe

5'-GTGGATGCTCTGTGTGCGTGCAAGATCCTTCAGGCCTTGTTCCAGTGTGA-3' (SEQ ID NO:45)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO710 gene using the probe oligonucleotide and one of the PCR primers.

- 5 RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

- 15 A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 67-69 and ending at the stop codon found at nucleotide positions 1765-1767 (Figure 26, SEQ ID NO:40). The predicted polypeptide precursor is 566 amino acids long, has a calculated molecular weight of approximately 65,555 daltons and an estimated pI of approximately 5.44. Analysis of the full-length PRO710 sequence shown in Figure 27 (SEQ ID NO:41) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 32, a transmembrane domain from about amino acid 454 to about amino acid 476, an aminoacyl-transfer RNA synthetase class-II signature sequence from about amino acid 6 to about amino acid 26 and potential N-glycosylation sites from about amino acid 111 to about amino acid 114, from about amino acid 146 to about amino acid 149 and from about amino acid 292 to about amino acid 295. Clone DNA44161-1434 has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209907.

- 25 Analysis of the amino acid sequence of the full-length PRO710 polypeptide suggests that it possesses significant sequence similarity to the CDC45 protein, thereby indicating that PRO710 may be a novel CDC45 homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO710 amino acid sequence and the following Dayhoff sequences, HSAJ3728_1, CEF34D10_1, S64939, UMUS0276_1, TRHY_SHEEP, CELT14E8_1, RNA1_YEAST, LVU89340_1, HSU80736_1 and CEZK337_2.

30 EXAMPLE 15: Isolation of cDNA clones Encoding Human PRO1151

- A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA40665. Based on the DNA40665 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1151.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCAGACGCTGCTCTTCGAAAGGGTC-3' (SEQ ID NO:48)

reverse PCR primer 5'-GGTCCCCGTAGGCCAGGTCCAGC-3' (SEQ ID NO:49)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40665 sequence which had the following nucleotide sequence

5 hybridization probe

5'-CTACTTCTTCAGCCTCAATGTGCACAGCTGGAATTACAAGGAGACGTACG-3' (SEQ ID NO:50)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1151 gene using the probe oligonucleotide and one of the PCR primers. RNA
10 for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1151 (designated herein as DNA44694-1500 [Figure 29, SEQ ID NO:46]; and the derived protein sequence for PRO1151.

The entire nucleotide sequence of DNA44694-1500 is shown in Figure 29 (SEQ ID NO:46). Clone
15 DNA44694-1500 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 272-274 and ending at the stop codon at nucleotide positions 1049-1051 (Figure 29). The predicted polypeptide precursor is 259 amino acids long (Figure 30). The full-length PRO1151 protein shown in Figure 30 has an estimated molecular weight of about 28,770 daltons and a pI of about 6.12. Analysis of the full-length PRO1151 sequence shown in Figure 30 (SEQ ID NO:47) evidences the presence of the following: a signal
20 peptide from about amino acid 1 to about amino acid 20, a potential N-glycosylation site from about amino acid 72 to about amino acid 75 and amino acid sequence blocks having homology to C1q domain-containing proteins from about amino acid 144 to about amino acid 178, from about amino acid 78 to about amino acid 111 and from about amino acid 84 to about amino acid 117. Clone UNQ581 (DNA44694-1500) has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203114.

25 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 30 (SEQ ID NO:47), evidenced significant homology between the PRO1151 amino acid sequence and the following Dayhoff sequences: ACR3_HUMAN, HP25_TAMAS, HUMC1QB2_1, P_R99306, CA1F_HUMAN, JX0369, CA24_HUMAN, S32436, P_R28916 and CA54_HUMAN.

30

EXAMPLE 16: Isolation of cDNA clones Encoding Human PRO1282

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA33778. Based on the DNA33778 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained
35 the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1282.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'TCTTCAGCCGCTTGCGCAACCTC3' (SEQ ID NO:53); and

reverse PCR primer 5'TTGCTCACATCCAGCTCCTGCAGG3' (SEQ ID NO:54).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA33778 sequence which had the following nucleotide sequence:

5 hybridization probe

5'TGGATGTTGTCCAGACAACCAGCTGGAGCTGTATCCGAGGC3' (SEQ ID NO:55).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1282 gene using the probe oligonucleotide and one of the PCR primers. RNA
10 for construction of the cDNA libraries was isolated from human fetal liver.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1282 (designated herein as DNA45495-1550 [Figure 31, SEQ ID NO:51]; and the derived protein sequence for PRO1282.

The entire coding sequence of PRO1282 is shown in Figure 31 (SEQ ID NO:51). Clone DNA45495-
15 1550 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 120-122, and an apparent stop codon at nucleotide positions 2139-2141 (SEQ ID NO:51). The predicted polypeptide precursor is 673 amino acids long. The signal peptide is at about amino acids 1-23; the transmembrane domain is at about amino acids 579-599; an EGF-like domain cysteine pattern signature starts at about amino acid 430; and leucine zipper patterns start at about amino acids 197 and 269 of SEQ ID NO:52,
20 see Figure 32. Clone DNA45495-1550 has been deposited with the ATCC and is assigned ATCC deposit no. 203156. The full-length PRO1282 protein shown in Figure 32 has an estimated molecular weight of about 71,655 daltons and a pI of about 7.8.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 32 (SEQ ID NO:52), revealed sequence identity
25 between the PRO1282 amino acid sequence and the following Dayhoff sequences (data from database incorporated by reference): AB007876_1, RNPLGPV_1, MUSLRRP_1, ALS_PAPPA, AC004142_1, ALS_HUMAN, AB014462_1, DMTARTAN_1, HSCHON03_1 and S46224.

EXAMPLE 17: Isolation of cDNA clones Encoding Human PRO358

30 Using the method described in Example 1 above, a single EST sequence was identified in the Incyte database, designated herein as INC3115949. Based on the INC3115949 EST sequence, oligonucleotides were synthesized to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for PRO358.

A pair of PCR primers (forward and reverse) were synthesized:

35 forward PCR primer 5'-TCCCACCAGGTATCATAACTGAA-3' (SEQ ID NO:58)

reverse PCR primer 5'-TTATAGACAATCTGTTCTCATCAGAGA-3' (SEQ ID NO:59)

A probe was also synthesized:

5'-AAAAAGCATACTTGGGAATGGCCCAAGGATAGGTGTAAATG-3' (SEQ ID NO:60)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO358 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow (LIB256). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO358 (Figure 33, SEQ ID NO:56) and the derived protein sequence for PRO358 (Figures 34, SEQ ID NO:57).

The entire nucleotide sequence of the clone identified (DNA47361-1154) is shown in Figure 33 (SEQ ID NO:56). Clone DNA47361-1154 contains a single open reading frame with an apparent translational initiation site (ATG start signal) at nucleotide positions underlined in Figure 33. The predicted polypeptide precursor is 811 amino acids long, including a putative signal sequence (amino acids 1 to 19), an extracellular domain (amino acids 20 to 575, including leucine rich repeats in the region from position 55 to position 575), a putative transmembrane domain (amino acids 576 to 595). Clone DNA47361-1249 has been deposited with ATCC and is assigned ATCC deposit no. 209431.

EXAMPLE 18: Isolation of cDNA clones Encoding Human PRO1310

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA37164. Based on the DNA37164 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1310.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'GTTCTCAATGAGCTACCCGTCCCC3' (SEQ ID NO:63) and
reverse PCR primer: 5'CGCGATGTAGTGGAACCTCGGGCTC3' (SEQ ID NO:64).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47394 sequence which had the following nucleotide sequence:

hybridization probe:

5'ATCCGCATAAACCCCTCAGTCCTGGTTTGATAATGGGAGCATCTGCATGAG3' (SEQ ID NO:65).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to

isolate clones encoding the PRO1310 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1310 and the derived protein sequence for PRO1310.

The entire coding sequence of PRO1310 is shown in Figures 35A-B (SEQ ID NO:61). Clone DNA47394-1572 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 326-328, and an apparent stop codon at nucleotide positions 2594-2596 (SEQ ID NO:61). The predicted polypeptide precursor is 765 amino acids long. The signal peptide is at about amino acids 1-25 of SEQ ID NO:62. Clone DNA47394-1572 has been deposited with ATCC and is assigned ATCC deposit no. 203109. The full-length PRO1310 protein shown in Figure 36 has an estimated molecular weight of about 85,898 daltons and a pI of about 6.87.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 36 (SEQ ID NO:62), revealed sequence identity between the PRO1310 amino acid sequence and the following Dayhoff sequences: AF017639_1, P_W36817, JC5256, CBPH_HUMAN, MMU23184_1, CBPN_HUMAN, HSU83411_1, CEF01D4_7, RNU62897_1 and P_W11851.

EXAMPLE 19: Isolation of cDNA Clones Encoding Human PRO698

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone whose sequence (herein designated as DNA39906) is shown in Figure 39 (SEQ ID NO:68). Based on the DNA39906 sequence shown in Figure 39, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO698. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-AGCTGTGGTCATGGTGGTGTGGTG-3' (SEQ ID NO:69)

reverse PCR primer 5'-CTACCTTGCCATAGGTGATCCGC-3' (SEQ ID NO:70)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA39906 sequence which had the following nucleotide sequence

hybridization probe

5'-CATCAGCAAACCGTCTGTGGTTCAGCTCAACTGGAGAGGGTT-3' (SEQ ID NO:71)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO698 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow tissue (LIB255). The cDNA

libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 14-16 and ending at the stop codon found at nucleotide positions 1544-1546 (Figure 37, SEQ ID NO:66). The predicted polypeptide precursor is 510 amino acids long, has a calculated molecular weight of approximately 57,280 daltons and an estimated pI of approximately 5.61.

Analysis of the full-length PRO698 sequence shown in Figure 38 (SEQ ID NO:67) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, potential N-glycosylation sites from about amino acid 72 to about amino acid 75, from about amino acid 136 to about amino acid 139, from about amino acid 193 to about amino acid 196, from about amino acid 253 to about amino acid 256, from about amino acid 352 to about amino acid 355 and from about amino acid 411 to about amino acid 414 an amino acid block having homology to legume lectin beta-chain proteins from about amino acid 20 to about amino acid 39 and an amino acid block having homology to the HBGF/FGF family of proteins from about amino acid 338 to about amino acid 365. Clone DNA48320-1433 has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209904.

Analysis of the amino acid sequence of the full-length PRO698 polypeptide suggests that it possesses significant sequence similarity to the olfactomedin protein, thereby indicating that PRO698 may be a novel olfactomedin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO698 amino acid sequence and the following Dayhoff sequences, OLFM_RANCA, I73637, AB006686S3_1, RNU78105_1, RNU72487_1, P_R98225, CELC48E7_4, CEF11C3_3, XLU85970_1 and S42257.

EXAMPLE 20: Isolation of cDNA Clones Encoding Human PRO732

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone whose sequence (herein designated as DNA42580) is shown in Figure 45 (SEQ ID NO:77). The DNA42580 sequence was then compared to a variety of known EST sequences to identify homologies. The EST databases employed included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

Using the above analysis, a consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is herein designated consen01. Proprietary Genentech EST sequences were employed in the consensus assembly and they are herein designated DNA20239 (Figure 42; SEQ ID NO:74), DNA38050 (Figure 43; SEQ ID NO:75) and DNA40683 (Figure 44; SEQ ID NO:76).

Based on the consen01 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO732. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

- forward PCR primer 5'-ATGTTTGTGTGGAAGTGCCCG-3' (SEQ ID NO:78)
 15 forward PCR primer 5'-GTCAACATGCTCCTCTGC-3' (SEQ ID NO:79)
reverse PCR primer 5'-AATCCATTGTGCACTGCAGCTCTAGG-3' (SEQ ID NO:80)
reverse PCR primer 5'-GAGCATGCCACCACTGGACTGAC-3' (SEQ ID NO:81)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA44143 sequence which had the following nucleotide sequence

- 20 hybridization probe
 5'-GCCGATGCTGCTCTAGTGGAAACAACCTCACTGTAAGTAGATTGATCTATGCAC-3' (SEQ ID NO:82)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO732 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB26). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 88-90 and ending at the stop codon found at nucleotide positions 1447-1449 (Figure 40, SEQ ID NO:72). The predicted polypeptide precursor is 453 amino acids long, has a calculated molecular weight of approximately 50,419 daltons and an estimated pI of approximately 5.78. Analysis of the full-length PRO732 sequence shown in Figure 41 (SEQ ID NO:73) evidences the presence of

the following: a signal peptide from about amino acid 1 to about amino acid 28, transmembrane domains from about amino acid 37 to about amino acid 57, from about amino acid 93 to about amino acid 109, from about amino acid 126 to about amino acid 148, from about amino acid 151 to about amino acid 172, from about amino acid 197 to about amino acid 215, from about amino acid 231 to about amino acid 245, from about amino acid 260 to about amino acid 279, from about amino acid 315 to about amino acid 333, from about amino acid 384 to about amino acid 403 and from about amino acid 422 to about amino acid 447, potential N-glycosylation sites from about amino acid 33 to about amino acid 36, from about amino acid 34 to about amino acid 37, from about amino acid 179 to about amino acid 183, from about amino acid 298 to about amino acid 301, from about amino acid 337 to about amino acid 340 and from about amino acid 406 to about amino acid 409, an amino acid block having homology to the MIP family of proteins from about amino acid 119 to about amino acid 149 and an amino acid block having homology to DNA/RNA non-specific endonuclease proteins from about amino acid 279 to about amino acid 286. Clone DNA48334-1435 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209924.

Analysis of the amino acid sequence of the full-length PRO732 polypeptide suggests that it possesses significant sequence similarity to the Diff33 protein, thereby indicating that PRO732 may be a novel Diff33 homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO732 amino acid sequence and the following Dayhoff sequences, HS179M20_2, MUSTETU_1, CER11H6_2, RATDRP_1, S51256, E69226, AE000869_1, JC4120, CYB_PARTE and P_R50619.

20 EXAMPLE 21: Isolation of cDNA clones Encoding Human PRO1120

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein consen0352. The consen0352 sequence was then extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above. The extended consensus sequence is designated herein as DNA34365. Based on the DNA34365 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1120.

PCR primers (forward and reverse) were synthesized:

forward PCR primers: 5'-GAAGCCGGCTGTCTGAATC-3' (SEQ ID NO:85),
 30 5'-GGCCAGCTATCTCCGCAG-3' (SEQ ID NO:86), 5'-AAGGGCCTGCAAGAGAAG-3' (SEQ ID NO:87),
 5'-CACTGGGACAACGTGTGGG-3' (SEQ ID NO:88),
 5'-CAGAGGCAACGTGGAGAG-3' (SEQ ID NO:89), and
 5'-AAGTATTGTCATACAGTGTTC-3' (SEQ ID NO:90);
reverse PCR primers: 5'-TAGTACTTGGGCACGAGGTTGGAG-3' (SEQ ID NO:91), and 5'-
 35 TCATACCAACTGCTGGTCATTGGC-3' (SEQ ID NO:92).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA34365 consensus sequence which had the following nucleotide sequence:

hybridization probe:

5'-CTCAAGCTGCTGGACACGGAGCGGCCGGTGAATCGGTTTCACTTG-3' (SEQ ID NO:93).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1120 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1120 (designated herein as DNA48606-1479 [Figures 46A-B, SEQ ID NO:83]; and the derived protein sequence for PRO1120.

The entire coding sequence of PRO1120 is shown in Figures 46A-B (SEQ ID NO:83). Clone DNA48606-1479 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 608-610 and an apparent stop codon at nucleotide positions 3209-3211. The predicted polypeptide precursor is 867 amino acids long. The full-length PRO1120 protein shown in Figure 47 has an estimated molecular weight of about 100,156 Daltons and a pI of about 9.44. Additional features of the PRO1120 polypeptide include a signal peptide at about amino acids 1-17; a sulfatase signature at about amino acids 86-98; regions of homology to sulfatases at about amino acids 87-106, 133-146, 216-229, 291-320, and 365-375; and potential N-glycosylation sites at about amino acids 65-68, 112-115, 132-135, 149-152, 171-174, 198-201, 241-245, 561-564, 608-611, 717-720, 754-757, and 764-767.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 47 (SEQ ID NO:84), revealed significant homology between the PRO1120 amino acid sequence and the following Dayhoff sequences: CELK09C4_1, GL6S_HUMAN, G65169, NCU89492_1, BCU44852_1, E64903, P_R51355, STS_HUMAN, GA6S_HUMAN, and IDS_MOUSE. Clone DNA48606-1479 was deposited with the ATCC on July 1, 1998, and is assigned ATCC deposit no. 203040.

25 EXAMPLE 22: Isolation of cDNA clones Encoding Human PRO537

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated as Incyte EST cluster no. 29605. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48350.

In light of an observed sequence homology between the DNA48350 consensus sequence and an EST sequence encompassed within the Merck EST clone no. R63443, the Merck EST clone R63443 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 48 and is herein designated as DNA49141-1431.

Clone DNA49141-1431 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 97-99 and ending at the stop codon at nucleotide positions 442-444 (Figure 48). The predicted polypeptide precursor is 115 amino acids long (Figure 49). The full-length PRO537 protein shown in Figure 49 has an estimated molecular weight of about 13,183 daltons and a pI of about 12.13. Analysis of the full-length PRO537 sequence shown in Figure 49 (SEQ ID NO:95) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31, a potential N-glycosylation site from about amino acid 44 to about amino acid 47, potential N-myristolation sites from about amino acid 3 to about amino acid 8 and from about amino acid 16 to about amino acid 21 and an amino acid block having homology to multicopper oxidase proteins from about amino acid 97 to about amino acid 105. Clone DNA49141-1431 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203003.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 49 (SEQ ID NO:95), evidenced homology between the PRO537 amino acid sequence and the following Dayhoff sequences: A54523, CELF22H10_2, FKH4_MOUSE, OTX1_HUMAN, URB1_USTMA, KNOB_PLAFN, A32895_1, AF036332_1, HRG_HUMAN and HRP3_PLAFS.

EXAMPLE 23: Isolation of cDNA clones Encoding Human PRO536

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as ss.clu2437.init. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48351.

In light of an observed sequence homology between the DNA48351 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H11129, the Merck EST clone H11129 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 50 and is herein designated as DNA49142-1430.

Clone DNA49142-1430 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 48-50 and ending at the stop codon at nucleotide positions 987-989 (Figure 50). The predicted polypeptide precursor is 313 amino acids long (Figure 51). The full-length PRO536 protein shown in Figure 51 has an estimated molecular weight of about 34,189 daltons and a pI of about 4.8. Analysis of the full-length PRO536 sequence shown in Figure 51 (SEQ ID NO:97) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, a potential N-glycosylation site from about amino acid 45 to about amino acid 48 and an amino acid sequence block having homology to sulfatase proteins from

about amino acid 16 to about amino acid 26. Clone DNA49142-1430 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203002.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 51 (SEQ ID NO:97), evidenced homology between the PRO536 amino acid sequence and the following Dayhoff sequences: APU46857_1, PK2_DICDI, H64743, F5114_18, CEAM_ECOLI, GEN14267, H64965, TCU39815_1, PSBJ_ODOSI and P_R06980.

EXAMPLE 24: Isolation of cDNA clones Encoding Human PRO535

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as ss.clu12694.init. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48352. Two proprietary Genentech EST sequences were employed in the assembly are herein shown in Figures 54 and 55.

In light of an observed sequence homology between the DNA48352 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H86994, the Merck EST clone H86994 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 52 and is herein designated as DNA49143-1429.

Clone DNA49143-1429 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 78-80 and ending at the stop codon at nucleotide positions 681-683 (Figure 52). The predicted polypeptide precursor is 201 amino acids long (Figure 53). The full-length PRO535 protein shown in Figure 53 has an estimated molecular weight of about 22,180 daltons and a pI of about 9.68. Analysis of the full-length PRO535 sequence shown in Figure 53 (SEQ ID NO:99) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, a transmembrane domain from about amino acid 155 to about amino acid 174, a potential N-glycosylation site from about amino acid 196 to about amino acid 199 and FKBP-type peptidyl-prolyl cis-trans isomer signature sequences from about amino acid 62 to about amino acid 77, from about amino acid 87 to about amino acid 123 and from about amino acid 128 to about amino acid 141. Clone DNA49143-1429 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203013.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST- sequence alignment analysis of the full-length sequence shown in Figure 53 (SEQ ID NO:99), evidenced homology between the PRO535 amino acid sequence and the following Dayhoff sequences: S71237, P_R93551, P_R28980, S71238, FKB2_HUMAN, CELC05C8_1, S55383, S72485, CELC50F2_6 and S75144.

EXAMPLE 25: Isolation of cDNA clones Encoding Human PRO718

A cDNA sequence isolated in the amylase screen described in Example 2 (human fetal lung library) above is herein designated DNA43512 (see Figure 62; SEQ ID NO:108). The DNA43512 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to
 5 identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA45625. Proprietary
 10 Genentech EST sequences were employed in the assembly and are herein shown in Figures 58-61.

Based on the DNA45625 sequence, oligonucleotide probes were generated and used to screen a human fetal lung library (LIB25) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science,
 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

15 PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GGGTGGATGGTACTGCTGCATCC-3' (SEQ ID NO:109)

reverse PCR primer 5'-TGTTGTGCTGTGGGAAATCAGATGTG-3' (SEQ ID NO:110)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA45625 sequence which had the following nucleotide sequence:

20 hybridization probe

5'-GTGTCTGGAGGCTGTGGCCGTTTTGTTTCTTGGGCTAAAATCGGG-3' (SEQ ID NO:111)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO718 gene using the probe oligonucleotide and one of the PCR primers.

25 A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 36-38 and ending at the stop codon found at nucleotide positions 607-609 (Figure 56; SEQ ID NO:102). The predicted polypeptide precursor is 157 amino acids long, has a calculated molecular weight of approximately 17,400 daltons and an estimated pI of approximately 5.78. Analysis of the full-length PRO718 sequence shown in Figure 57 (SEQ ID NO:103) evidences the presence of
 30 the following: a type II transmembrane domain from about amino acid 21 to about amino acid 40, and other transmembrane domains at about amino acid 58 to about amino acid 78, about amino acid 95 to about amino acid 114, and about amino acid 127 to about amino acid 147; a cell attachment sequence from about amino acid 79 to about amino acid 81; and a potential N-glycosylation site from about amino acid 53 to about amino acid 56. Clone DNA49647-1398 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no.
 35 209919.

Analysis of the amino acid sequence of the full-length PRO718 polypeptide suggests that it possesses no significant sequence similarity to any known protein. However, an analysis of the Dayhoff database (version

35.45 SwissProt 35) evidenced some degree of homology between the PRO718 amino acid sequence and the following Dayhoff sequences: AF045606_1, AF039906_1, SPBC8D2_2, S63441, F64728, COX1_TRYBB, F64375, E64173, RPYGJT_3, MTCY261_23.

EXAMPLE 26: Isolation of cDNA clones Encoding Human PRO872

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence designated herein as clu120709.init. The clu120709.init sequence was then compared a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or
10 in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48254.

In light of an observed sequence homology between the DNA48254 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3438068, the Incyte EST clone 3438068 was purchased
15 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 63 and is the full-length DNA sequence for PRO872. Clone DNA49819-1439 was deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209931.

The entire nucleotide sequence of DNA49819-1439 is shown in Figure 63 (SEQ ID NO:112). Clone
20 DNA49819-1439 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 14-16 and ending at the stop codon at nucleotide positions 1844-1846 (Figure 63). The predicted polypeptide precursor is 610 amino acids long (Figure 64). The full-length PRO872 protein shown in Figure 64 has an estimated molecular weight of about 66,820 daltons and a pI of about 8.65. Analysis of the full-length PRO872 sequence shown in Figure 64 (SEQ ID NO:113) evidences the presence of the following features: a
25 signal peptide at amino acid 1 to about 18, putative transmembrane domains at about amino acids 70-87, 200-222 and 568-588; sequence identity with bacterial-type phytoene dehydrogenase protein at about amino acids 71-105; sequence identity with a regulator of chromosome condensation (RCC1) signature 2 at about amino acids 201-211; leucine zipper patterns at about amino acids 214-235, 221-242, 228-249 and 364-385; a potential N-glycosylation site at about amino acids 271-274; and a glycosaminoglycan attachment site at about amino acids
30 75-78. Analysis of the amino acid sequence of the full-length PRO872 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO872 amino acid sequence and the following Dayhoff sequences: PRCRTI_1, S75951, S74689, CELF37C4_3, CRTI_RHOCA, S76617, YNI2_METTL, MTV014_14, AOFB_HUMAN, and MMU70429_1.

35 **EXAMPLE 27: Isolation of cDNA clones Encoding Human PRO1063**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as ss.clu119743.init. The Incyte EST cluster sequence

ss.clu119743.init sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48288.

In light of an observed sequence homology between the DNA48288 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2783726, the Incyte EST clone 2783726 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 65 and is herein designated DNA49820-1427.

The full length clone shown in Figure 65 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 90-92 and ending at the stop codon found at nucleotide positions 993-995 (Figure 65; SEQ ID NO:114). The predicted polypeptide precursor is 301 amino acids long, has a calculated molecular weight of approximately 33,530 daltons and an estimated pI of approximately 4.80. Analysis of the full-length PRO1063 sequence shown in Figure 66 (SEQ ID NO:115) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, potential N-glycosylation sites from about amino acid 195 to about amino acid 198, from about amino acid 217 to about amino acid 220 and from about amino acid 272 to about amino acid 275, a glycosaminoglycan attachment site from about amino acid 267 to about amino acid 270, a microbodies C-terminal targeting signal site from about amino acid 299 to about amino acid 301, a type II fibronectin collagen-binding domain homology sequence from about amino acid 127 to about amino acid 168 and a fructose-bisphosphate aldolase class II protein homology sequence from about amino acid 101 to about amino acid 118. Clone DNA49820-1427 has been deposited with the ATCC on June 2, 1998 and is assigned ATCC deposit no. 209932.

Analysis of the amino acid sequence of the full-length PRO1063 polypeptide suggests that it possesses sequence similarity to the human type IV collagenase protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1063 amino acid sequence and the following Dayhoff sequences, S68303, CFU68533_1, P_P91139, RNU65656_1, PA2R_RABIT, MMU56734_1, FINC_XENLA, A48925, P_R92778 and FA12_HUMAN.

EXAMPLE 28: Isolation of cDNA clones Encoding Human PRO619

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as 88434. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score

of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1656694, the Incyte EST clone 1656694 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 67 and is herein designated as DNA49821-1562.

The full length clone shown in Figure 67 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 81-83 and ending at the stop codon found at nucleotide positions 450-452 (Figure 67; SEQ ID NO:116). The predicted polypeptide precursor (Figure 68, SEQ ID NO:117) is 123 amino acids long including a predicted signal peptide at about amino acids 1-20. PRO619 has a calculated molecular weight of approximately 13,710 daltons and an estimated pI of approximately 5.19. Clone DNA49821-1562 was deposited with the ATCC on June 16, 1998 and is assigned ATCC deposit no. 209981.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 68 (SEQ ID NO:117), revealed significant homology between the PRO619 amino acid sequence and the following Dayhoff sequences: S35302, D87009_1, HSU93494_1, HUMIGLAM5_1, D86999_2, HUMIGLYM1_1, HUMIGLYMKE_1, A29491_1, A29498_1, and VPR2_MOUSE.

EXAMPLE 29: Isolation of cDNA clones Encoding Human PRO943

A consensus DNA sequence encoding PRO943 was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence was then extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above. The extended consensus sequence is herein designated DNA36360. Based on the DNA36360 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO943.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CGAGATGACGCCGAGCCCC-3' (SEQ ID NO:120)

reverse PCR primer 5'-CGGTTCGACACGCGGCAGGTG-3' (SEQ ID NO:121)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36360 sequence which had the following nucleotide sequence

hybridization probe

5'-TGCTGCTCCTGCTGCCGCCGCTGCTGCTGGGGGCCTTCCCGCCGG-3' (SEQ ID NO:122)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO943 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO943 (designated herein as DNA52192-1369 [Figure 69, SEQ ID NO:118]) and the derived protein sequence for PRO943.

The entire nucleotide sequence of DNA52192-1369 is shown in Figure 69 (SEQ ID NO:118). Clone DNA52192-1369 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 150-152 and ending at the stop codon at nucleotide positions 1662-1664 (Figure 69). The predicted polypeptide precursor is 504 amino acids long (Figure 70). The full-length PRO943 protein shown in Figure 70 has an estimated molecular weight of about 54,537 daltons and a pI of about 10.04. Analysis of the full-length PRO943 sequence shown in Figure 70 (SEQ ID NO:119) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 17, a transmembrane domain from about amino acid 376 to about amino acid 396, tyrosine kinase phosphorylation sites from about amino acid 212 to about amino acid 219 and from about amino acid 329 to about amino acid 336, potential N-glycosylation sites from about amino acid 111 to about amino acid 114, from about amino acid 231 to about amino acid 234, from about amino acid 255 to about amino acid 258 and from about amino acid 293 to about amino acid 296 and an immunoglobulin and MHC protein sequence homology block from about amino acid 219 to about amino acid 236. Clone DNA52192-1369 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203042.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 70 (SEQ ID NO:119), evidenced significant homology between the PRO943 amino acid sequence and the following Dayhoff sequences: B49151, A39752, FGR1_XENLA, S38579, RATHBFGFRB_1, TVHU2F, FGR2_MOUSE, CEK3_CHICK, P_R21080 and A27171_1.

EXAMPLE 30: Isolation of cDNA clones Encoding Human PRO1188

A consensus DNA sequence was assembled relative to other EST sequences using the program "phrap" as described in Example 1 above. This consensus sequence is designated herein as DNA45679. Based on the DNA45679 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1188.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTGGTGCCTCAACAGGGAGCAG-3' (SEQ ID NO:125)

reverse PCR primer 5'-CCATTGTGCAGGTCAGGTCACAG-3' (SEQ ID NO:126)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45679 sequence which had the following nucleotide sequence:

hybridization probe

5'-CTGGAGCAAGTGCTCAGCTGCCTGTGGTCAGACTGGGGTC-3' (SEQ ID NO:127)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1188 gene using the probe oligonucleotide and one of the PCR primers. RNA

for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1188 (designated herein as DNA52598-1518 [Figure 71, SEQ ID NO:123]); and the derived protein sequence for PRO1188.

The entire coding sequence of PRO1188 is shown in Figure 71 (SEQ ID NO:123). Clone DNA52598-1518 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 136-138 and an apparent stop codon at nucleotide positions 3688-3690. The predicted polypeptide precursor is 1184 amino acids long. The full-length PRO1188 protein shown in Figure 72 has an estimated molecular weight of about 132,582 Daltons and a pI of about 8.80. Additional features include: a signal peptide at about amino acids 1-31; an ATP/GTP binding site motif A (P-loop) at about amino acids 266-273; an aldehyde dehydrogenases cysteine active site at about amino acids 188-199; growth factor and cytokines receptors family signature 2 at about amino acids 153-159; and potential N-glycosylation sites at about amino acids 129-132, 132-135, 346-349, 420-423, 550-553, 631-634, 1000-1003, and 1056-1059.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 72 (SEQ ID NO:124), revealed significant homology between the PRO1188 amino acid sequence and the following Dayhoff sequences: SSU83114_1, S56015, CET21B6_4, CELT19D2_1, and TSP1_MOUSE.

Clone DNA52598-1518 has been deposited with ATCC and is assigned ATCC deposit no 203107.

EXAMPLE 31: Isolation of cDNA clones Encoding Human PRO1133

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This sequence was extended using repeated cycles of phrap. The extended consensus sequence is designated herein DNA38102. Based on the DNA38102 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1133.

PCR primers (two forward and one reverse) were synthesized:
forward PCR primer 1 5'-TCGATTATGGACGAACATGGCAGC-3' (SEQ ID NO:130);
forward PCR primer 2 5'-TTCTGAGATCCCTCATCCTC-3' (SEQ ID NO:131); and
reverse primer 5'-AGGTTTCAGGGACAGCAAGTTTGGG-3' (SEQ ID NO:132).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA38102 sequence which had the following nucleotide sequence:

hybridization probe

5'TTTGCTGGACCTCGGCTACGGAATTGGCTTCCCTCTACGGACAGCTGGAT3' (SEQ ID NO:133).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with a PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1133 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1133 and the derived protein sequence for PRO1133.

The entire coding sequence of PRO1133 is shown in Figure 73 (SEQ ID NO:128). Clone DNA53913-1490 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 266-268 and an apparent stop codon at nucleotide positions 1580-1582 of SEQ ID NO:128. The predicted polypeptide precursor is 438 amino acids long. The signal peptide is at amino acids 1-18 of SEQ ID NO:129. EGF-like domain cysteine pattern signatures start at 315 and 385 of SEQ ID NO:129 as shown in Figure 74. Clone DNA53913-1490 has been deposited with ATCC and is assigned ATCC deposit no. 203162. The full-length PRO1133 protein shown in Figure 74 has an estimated molecular weight of about 49,260 daltons and a pI of about 6.15.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 74 (SEQ ID NO:129), revealed some sequence identity between the PRO1133 amino acid sequence and the following Dayhoff sequences (data from the database incorporated herein): AF002717_1, LMG1_HUMAN, B54665, UNC6_CAEEL, LML1_CAEEL, LMA5_MOUSE, MMU88353_1, LMA1_HUMAN, HSLN2C64_1 and AF005258_1.

EXAMPLE 32: Isolation of cDNA clones Encoding Human PRO784

An initial DNA sequence (SEQ ID NO:136), referred to herein as DNA44661 and shown in Figure 77, was identified using a yeast screen, in a human fetal lung cDNA library that preferentially represents the 5' ends of the primary cDNA clones. DNA44661 was then compared to ESTs from public databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. The ESTs were then clustered and assembled into a consensus DNA sequence using the computer program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained is designated herein as "DNA45463". Based on the DNA45463 consensus sequence, oligonucleotides were synthesized for use as probes to isolate a clone of the full-length coding sequence for PRO784 from a human fetal lung cDNA library.

The full length DNA53978-1443 clone shown in Figure 75 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 37-39 and ending at the stop codon found at nucleotide positions 821-823 (Figure 75; SEQ ID NO:134). The predicted polypeptide precursor (Figure 76, SEQ ID NO:135) is 228 amino acids long. PRO784 has a calculated molecular weight of approximately 25,735 Daltons and an estimated pI of approximately 5.45. PRO784 has the following features: a signal peptide at about amino acid 1 to about 15; transmembrane domains at about amino acids 68 to about 87 and at about 183 to about 204; potential N-myristoylation sites at about amino acids 15-20, 51-56, 66-60, 163-168, and 206-211; and an RNP-1 protein RNA-binding region at about amino acids 108 to about 117.

Clone DNA53978-1443 was deposited with ATCC on June 16, 1998, and is assigned ATCC deposit no. 209983.

Based on a BLAST and FastA sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO784 shows amino acid sequence identity to the following proteins: RNU42209_1,

MMU91538_1, CGU91742_1, CELF55A4_6, SC22_YEAST, and F48188.

EXAMPLE 33: Isolation of cDNA Clones Encoding Human PRO783

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone, designated herein as DNA45201 (Figure 80; SEQ ID NO:139).

The DNA45201 sequence was then used to search expressed sequence tag (EST) databases for the presence of potential homologies. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained is herein designated as "consen01". A proprietary Genentech EST sequence was used in the consensus assembly and is herein designated as DNA14575 (Figure 81; SEQ ID NO:140).

Based on the consen01 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO783. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GACTGTATCTGAGCCCCAGACTGC-3' (SEQ ID NO:141),

forward PCR primer 5'-TCAGCAATGAGGTGCTGCTC-3' (SEQ ID NO:142), and

reverse PCR primer 5'-TGAGGAAGATGAGGGACAGGTTGG-3' (SEQ ID NO:143).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consen01 sequence which had the following nucleotide sequence:

hybridization probe

5'-TATGGAAGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCC-3' (SEQ ID NO:144).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with a PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO783 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB228). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science,

253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO783 [herein designated as DNA53996-1442] (SEQ ID NO:137) and the derived protein sequence for PRO783.

The entire nucleotide sequence of DNA53996-1442 is shown in Figure 78 (SEQ ID NO:137). Clone
 5 DNA53996-1442 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 310-312 and ending at the stop codon at nucleotide positions 1777-1779 (Figure 78). The predicted polypeptide precursor is 489 amino acids long (Figure 79). The full-length PRO783 protein shown in Figure 79 has an estimated molecular weight of about 55,219 daltons and a pI of about 8.47. Analysis of the full-length PRO783 sequence shown in Figure 79 (SEQ ID NO:138) evidences the presence of the following features:
 10 transmembrane domains located at about amino acids 23-42, 67-89, 111-135, 154-176, 194-218, 296-319, 348-370, 387-410 and 427-452; leucine zipper patterns located at about amino acids 263-283 and 399-420; a potential tyrosine kinase phosphorylation site at about amino acids 180-187; potential N-glycosylation sites at about amino acids 105 -108 and 121-124; potential cAMP- and a cGMP-dependent protein kinase phosphorylation site at about amino acids 288-291; and a region having sequence identity with bacterial
 15 rhodopsins retinal binding site protein at about amino acids 190-218.

An analysis of the Dayhoff database (version 35.45 SwissProt 35) shows some sequence identity between the PRO783 amino acid sequence and the following Dayhoff sequences: YNC2_CAEEL, D64048, ATAC002332_3F4P9.3, NY2R_SHEEP, and VSH_MUMPA.

Clone DNA53996-1442 was deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit
 20 no. 209921.

EXAMPLE 34: Isolation of cDNA Clones Encoding Human PRO820

An expressed sequence tag (EST) DNA database (Merck/Wash. U) was searched and an EST designated
 25 EST no. AA504080, Merck clone 825136, was identified (library 312, human B-cell tonsil). Homology searches revealed that this EST showed sequence identity with low affinity immunoglobulin gamma Fc receptor II. DNA sequencing gave the full-length DNA sequence for PRO820 and the derived protein sequence for PRO820.

The entire nucleotide sequence of DNA56041-1416 is shown in Figure 82 (SEQ ID NO:145). Clone
 30 DNA56041-1416 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 115-117 and ending at the stop codon at nucleotide positions 487-489 (Figure 82). The predicted polypeptide precursor is 124 amino acids long (Figure 83). The full-length PRO820 protein shown in Figure 83 has an estimated molecular weight of about 14,080 daltons and a pI of about 7.48. Clone DNA56041-1416 has been deposited with ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Still analyzing the amino acid sequence of SEQ ID NO:146, the putative signal peptide is at about amino
 35 acids 1-15 of SEQ ID NO:146. Protein kinase C phosphorylation sites are at about amino acids 20-22 and 43-45 of SEQ ID NO:146. An N-myristoylation site is at about amino acids 89-94 of SEQ ID NO:146. An immunoglobulin and major histocompatibility complex domain is at about amino acids 83-90 of SEQ ID NO:146.

The corresponding nucleotides can be routinely determined given the sequences provided herein.

EXAMPLE 35: Isolation of cDNA Clones Encoding Human PRO1080

A consensus DNA sequence was assembled relative to other EST sequences using phrap and was extended using repeated cycles of BLAST and phrap so as to extend the consensus sequence as far as possible using the sources of the EST sequences as described in Example 1 above. The consensus sequence is designated herein as DNA52640. An EST proprietary to Genentech was employed in the consensus assembly and is herein designated as DNA36527 (Figure 86; SEQ ID NO:149).

In light of an observed sequence homology between the DNA36527 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 526423, the Merck EST clone 526423 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 84 and is herein designated as DNA56047-1456.

The entire nucleotide sequence of DNA56047-1456 is shown in Figure 84 (SEQ ID NO:147). Clone DNA56047-1456 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 159-161 and ending at the stop codon at nucleotide positions 1233-1235 of SEQ ID NO:147 (Figure 84). The predicted polypeptide precursor is 358 amino acids long (Figure 85). The full-length PRO1080 protein shown in Figure 85 has an estimated molecular weight of about 40,514 daltons and a pI of about 6.08. Clone DNA56047-1456 has been deposited with ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Also shown in Figure 85 are the approximate locations of the signal peptide, cell attachment site, Nt-DnaJ domain signature, region having sequence identity with Nt-DnaJ domain proteins, and N-glycosylation sites. The corresponding nucleic acids of these amino acid sequences and others provided herein can be routinely determined by the information provided herein.

EXAMPLE 36: Isolation of cDNA Clones Encoding Human PRO1079

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above, and is herein designated DNA52714. Based on information provided by the assembly, the clone for Merck EST no. HO6898 was obtained and sequenced, thereby giving the nucleotide sequence designated herein as DNA56050-1455. The entire nucleotide sequence of DNA56050-1455 is shown in Figure 87 (SEQ ID NO:150). Clone DNA56050-1455 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 183-185 and ending at the stop codon at nucleotide positions 861-863 (Figure 87). The predicted polypeptide precursor is 226 amino acids long (Figure 88). The full-length PRO1079 protein shown in Figure 88 has an estimated molecular weight of about 24,611 Daltons and a pI of about 4.85. Analysis of the full-length PRO1079 sequence shown in Figure 88 (SEQ ID NO:3) evidences the presence of the following features: a signal peptide at about amino acid 1-29; potential N-myristoylation sites at about amino acids 10-15, and 51-56; homology to photosystem I psaG and psaK proteins at about amino acids 2 to 20; and homology to prolyl endopeptidase family serine proteins at about amino acids 150 to 163.

Analysis of the amino acid sequence of the full-length PRO1079 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO1079 amino acid sequence and the following Dayhoff sequences: CEK10C3_4, MMU50734_1, D69503, AF051149_1, and VSMP_CVMS.

Clone UNQ536 (DNA56050-1455) was deposited with the ATCC on June 22, 1998, and is assigned ATCC deposit no. 203011.

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EXAMPLE 37: Isolation of cDNA clones Encoding Human PRO793

A cDNA clone (DNA56110-1437) encoding a native human PRO793 polypeptide was identified by a yeast screen, in a human skin tumor cDNA library that preferentially represents the 5' ends of the primary cDNA clones. The yeast screen employed identified a single EST clone designated herein as DNA50177 (Figure 91; SEQ ID NO:154). The DNA50177 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA50972.

In light of an observed sequence homology between the DNA50972 consensus sequence and an EST sequence encompassed within the Merck EST clone no. N33874, the Merck EST clone N33874 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 89 and is herein designated as DNA56110-1437.

The full-length DNA56110-1437 clone shown in Figure 89 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 77-79 and ending at the stop codon at nucleotide positions 491-493 (Figure 89). The predicted polypeptide precursor is 138 amino acids long (Figure 90). The full-length PRO793 protein shown in Figure 90 has an estimated molecular weight of about 15,426 daltons and a pI of about 10.67. Analysis of the full-length PRO793 sequence shown in Figure 90 (SEQ ID NO:153) evidences the presence of the following: transmembrane domains from about amino acid 12 to about amino acid 30, from about amino acid 33 to about amino acid 52, from about amino acid 69 to about amino acid 89 and from about amino acid 93 to about amino acid 109, potential N-myristylation sites from about amino acid 11 to about amino acid 16, from about amino acid 51 to about amino acid 56 and from about amino acid 116 to about amino acid 121 and an amino acid sequence block having homology to an aminoacyl-transfer RNA synthetase class-II protein from about amino acid 49 to about amino acid 59. Clone DNA56110-1437 has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203113.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 90 (SEQ ID NO:153), evidenced certain homology between the PRO793 amino acid sequence and the following Dayhoff sequences: S47453, AF015193_12, MTEHGNS9_2, E64030, H69784, D64995, CD53_MOUSE, GEN8006, AE001138_7 and COX2_STRPU.

EXAMPLE 38: Isolation of cDNA Clones Encoding Human PRO1016

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. The consensus sequence obtained is herein designated DNA53502.

In light of an observed sequence homology between the DNA53502 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 38680, the Merck EST clone 38680 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 92.

The entire nucleotide sequence of DNA56113-1378 is shown in Figure 92 (SEQ ID NO:155). Clone DNA56113-1378 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 168-170 and ending at the stop codon at nucleotide positions 1302-1304 (Figure 92). The predicted polypeptide precursor is 378 amino acids long (Figure 93). The full-length PRO1016 protein shown in Figure 93 has an estimated molecular weight of about 44,021 daltons and a pI of about 9.07. Clone DNA56113-1378 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO1016 polypeptide suggests that portions of it possess sequence identity with acyltransferase, thereby indicating that PRO1016 may be a novel acyltransferase.

Still analyzing the amino acid sequence of SEQ ID NO:156, the putative signal peptide is at about amino acids 1-18 of SEQ ID NO:156. The transmembrane domain(s) are at about amino acids 332-352 and 305-330 of SEQ ID NO:156. The fructose-bisphosphate aldolase class-II protein homology sequence is at about amino acids 73-90 of SEQ ID NO:156. The extradiol ring-cleavage dioxygenase protein is at about amino acids 252-275 of SEQ ID NO:156. The corresponding nucleotides can be routinely determined given the sequences provided herein.

The specific Dayhoff database designation names of sequences to which PRO1016 has sequence identity with include the following: S52645, P_R59712, P_R99249, P_R59713, BNAGPATRF_1, CELT05H4_15 and CELZK40_1.

EXAMPLE 39: Isolation of cDNA Encoding Human PRO1013

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. The consensus DNA sequence was then extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences.

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3107695, the Incyte EST clone 3107695 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 94 and is herein designated as DNA56410-1414.

The entire nucleotide sequence of DNA56410-1414 is shown in Figure 94 (SEQ ID NO:157). Clone DNA56410-1414 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 17-19 and ending at the stop codon at nucleotide positions 1244-1246 (Figure 94). The predicted

polypeptide precursor is 409 amino acids long (Figure 95). The full-length PRO1013 protein shown in Figure 95 has an estimated molecular weight of about 46,662 daltons and a pI of about 7.18. Clone DNA56410-1414 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

5 Still analyzing the amino acid sequence of SEQ ID NO:158, the putative signal peptide is at about amino acids 1-19 of SEQ ID NO:158. N-glycosylation sites are at about amino acids 75-78 and 322-325 of SEQ ID NO:158. An N-myristoylation site is at about amino acids 184-189 of SEQ ID NO:158. A growth factor and cytokine receptor family domain is at about amino acids 134-149 of SEQ ID NO:158. The corresponding nucleotides can be routinely determined given the sequences provided herein.

10 Blast analysis showed some sequence identity with other proteins. Specifically, PRO1013 has some sequence identity with at least the Dayhoff sequences designated: D63877_1; MHU22019_1, AE000730_10, and AF019079_1.

EXAMPLE 40: Isolation of cDNA Clones Encoding Human PRO937

15 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. That consensus sequence is herein designated DNA49651. Based on the DNA49651 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO937.

PCR primers (forward and reverse) were synthesized:

20 forward PCR primer 5'-CTCCGTGGTAAACCCACAGCCC-3' (SEQ ID NO:161); and
reverse PCR primer 5'-TCACATCGATGGGATCCATGACCG-3' (SEQ ID NO:162).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA48651 sequence which had the following nucleotide sequence:

25 hybridization probe
 5'-GGTCTCGTGACTGTGAAGCCATGTTACAACACTGCTCAAACATCATGAG-3' (SEQ ID NO:163).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO937 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

30 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO937 [herein designated as DNA56436-1448] (SEQ ID NO:159) and the derived protein sequence for PRO937.

35 The entire nucleotide sequence of DNA56436-1448 is shown in Figure 96 (SEQ ID NO:159). It contains a single open reading frame having an apparent translational initiation site at nucleotide positions 499-501 and ending at the stop codon found at nucleotide positions 2167-2169 (Figure 96, SEQ ID NO:159). The predicted polypeptide precursor is 556 amino acids long, has a calculated molecular weight of approximately 62,412 daltons and an estimated pI of approximately 6.62. Analysis of the full-length PRO937 sequence shown

in Figure 97 (SEQ ID NO:160) evidences the presence of the following features: signal peptide at about amino acids 1-22; ATP/GTP-binding site motif A (P-loop) at about amino acids 515-523; a potential N-glycosylation site at about amino acids 514-517; and sites of glypican homology at about amino acids 54-74, 106-156, 238-279, 309-345, 423-459, and 468-505.

5 Clone DNA56436-1448 has been deposited with ATCC on May 27, 1998, and is assigned ATCC deposit no. 209902.

Analysis of the amino acid sequence of the full-length PRO937 polypeptide suggests that it possesses significant sequence similarity to glypican proteins, thereby indicating that PRO937 may be a novel glypican protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO937 amino acid sequence and the following Dayhoff sequences:

10 GPCCK_MOUSE, GPC2_RAT, GPC5_HUMAN, GPC3_HUMAN, P_R30168, CEC03H12_2, GEN13820, HS119E23_1, HDAC_DROME, and AF017637_1.

EXAMPLE 41: Isolation of cDNA clones Encoding Human PRO842

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single

15 Incyte EST cluster sequence designated herein as Incyte EST cluster sequence no. 69572. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a

20 BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA54230.

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA477092, the Merck EST clone AA477092 was purchased and

25 the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 98 and is herein designated as DNA56855-1447.

The full length clone shown in Figure 98 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 153-155 and ending at the stop codon found at nucleotide positions 510-512 (Figure 98; SEQ ID NO:164). The predicted polypeptide precursor (Figure 99, SEQ ID

30 NO:165) is 119 amino acids long. PRO842 has a calculated molecular weight of approximately 13,819 Daltons and an estimated pI of approximately 11.16. Other features of PRO842 include a signal peptide at about amino acids 1-22, a potential protein kinase C phosphorylation site at about amino acids 39-41 and two potential N-myristoylation sites at about amino acids 27-32 and about amino acids 46-51.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence

35 alignment analysis of the full-length sequence shown in Figure 98 (SEQ ID NO:164), evidenced some homology between the PRO842 amino acid sequence and the following Dayhoff sequences: CEZK131_11, P_R80843, RAT5HT2X_1, S81882_1, A60912, MCU60315_137MC137L, U93422_1, p_P91996, U93462_1, and

ZN18_HUMAN.

Clone DNA56855-1447 was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no. 203004.

EXAMPLE 42: Isolation of cDNA clones Encoding Human PRO839

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte LIFESEQ® database, designated Incyte EST Cluster No. 24479. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using
10 the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55709.

15 In light of an observed sequence homology between the DNA55709 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 754525, the Merck EST clone 754525 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 100 and is herein designated as DNA56859-1445.

The full length clone shown in Figure 100 contained a single open reading frame with an apparent
20 translational initiation site at nucleotide positions 2-4 and ending at the stop codon found at nucleotide positions 263-265 (Figure 100; SEQ ID NO:166). The predicted polypeptide precursor (Figure 101, SEQ ID NO:167) is 87 amino acids long. PRO839 has a calculated molecular weight of approximately 9,719 Daltons and an estimated pI of approximately 4.67. Other features of PRO839 include a signal peptide at about amino acids 1-23, potential protein kinase C phosphorylation sites at about amino acids 37-39 and about amino acids 85-87,
25 a potential casein kinase II phosphorylation site at about amino acids 37-40, sequence identity with ribonucleotide reductase large subunit protein at about amino acids 50-60, and sequence identity with eukaryotic RNA-binding region RNP-1 proteins at about amino acids 70-79.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 101 (SEQ ID NO:167), evidenced some
30 homology between the PRO839 amino acid sequence and the following Dayhoff sequences: CD14_MOUSE, XPR6_YARLI, HS714385_1, S49783, BB19_RABIT, GVPH-HALME, AB003135_1, P_R85453, LUU27081_2, and TP2B_MOUSE.

Clone DNA56859-1445 was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no.209019.

EXAMPLE 43: Isolation of cDNA Clones Encoding Human PRO1180

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence (Incyte EST cluster sequence no. 14732). The Incyte EST cluster sequence no. 14732 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55711.

In light of an observed sequence homology between the DNA55711 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T60981, the Merck EST clone T60981 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 102 and is herein designated DNA56860-1510.

The full length clone shown in Figure 102 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 78-80 and ending at the stop codon found at nucleotide positions 909-911 (Figure 102; SEQ ID NO:168). The predicted polypeptide precursor is 277 amino acids long, has a calculated molecular weight of approximately 31,416 daltons and an estimated pI of approximately 8.88. Analysis of the full-length PRO1180 sequence shown in Figure 103 (SEQ ID NO:169) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, a leucine zipper pattern sequence from about amino acid 10 to about amino acid 31, and potential N-myristolation sited from about amino acid 64 to about amino acid 69, from about amino acid 78 to about amino acid 83, from about amino acid 80 to about amino acid 85, from about amino acid 91 to about amino acid 96 and from about amino acid 201 to about amino acid 206. Clone DNA56860-1510 has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209952.

Analysis of the amino acid sequence of the full-length PRO1180 polypeptide suggests that it possesses sequence similarity to the methyltransferase family of proteins. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1180 amino acid sequence and the following Dayhoff sequences, MTCI65_14, D69267, YH09_YEAST, BIOC_SERMA, ATAC00448415T1D16.16, SHGCPIR_18, SPBC3B9_4, AB009504_14, P_W17977 and A69952.

EXAMPLE 44: Isolation of cDNA clones Encoding Human PRO1134

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 7511. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or

in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55725. Two proprietary Genentech EST sequences were employed in the assembly and are shown in Figure 106 (SEQ ID NO:172) and Figure 107 (SEQ ID NO:173).

5 In light of an observed sequence homology between the DNA55725 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H94897, the Merck EST clone H94897 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 106 and is herein designated as DNA56865-1491.

10 Clone DNA56865-1491 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 153-155 and ending at the stop codon at nucleotide positions 1266-1268 (Figure 104). The predicted polypeptide precursor is 371 amino acids long (Figure 105). The full-length PRO1134 protein shown in Figure 105 has an estimated molecular weight of about 41,935 daltons and a pI of about 9.58. Analysis of the full-length PRO1134 sequence shown in Figure 105 (SEQ ID NO:171) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, potential N-glycosylation sites from
15 about amino acid 103 to about amino acid 106, from about amino acid 249 to about amino acid 252 and from about amino acid 257 to about amino acid 260, and an amino acid block having homology to tyrosinase CuA-binding region proteins from about amino acid 280 to about amino acid 306. Clone DNA56865-1491 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203022.

20 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 105 (SEQ ID NO:171), evidenced significant homology between the PRO1134 amino acid sequence and the following Dayhoff sequences: F20P5_18, AC002396_10, S47847, C64146, GSPA_BACSU, P_W10564, RFAI_ECOLI, Y258_HAEIN, RFAJ_SALTY and P_R32985.

25 EXAMPLE 45: Isolation of cDNA clones Encoding Human PRO830

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incytedatabase, designated 20251. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing
30 homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55733.

35 In light of an observed sequence homology between the DNA55733 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H78534, the Merck EST clone H78534 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 108 and is herein designated as DNA56866-1342.

Clone DNA56866-1342 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 154-156 and ending at the stop codon at nucleotide positions 415-417 (Figure 108). The predicted polypeptide precursor is 87 amino acids long (Figure 109). The full-length PRO830 protein shown in Figure 109 has an estimated molecular weight of about 9,272 daltons and a pI of about 9.19. Analysis of the full-length PRO830 sequence shown in Figure 109 (SEQ ID NO:175) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 33, potential N-myristoylation sites from about amino acid 2 to about amino acid 7 and from about amino acid 8 to about amino acid 13 and a thioredoxin family of proteins homology block from about amino acid 23 to about amino acid 39. Clone UNQ470 (DNA56866-1342) has been deposited with ATCC on June 22, 1998 and is assigned ATCC deposit no. 203023.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 109 (SEQ ID NO:175), evidenced significant homology between the PRO830 amino acid sequence and the following Dayhoff sequences: HSU88154_1, HSU88153_1, SAPKSGENE_1, HPU31791_5, GGCNOT2_1, CPU91421_1, CHKESTPC09_1, PQ0769, U97553_79 and B60095.

EXAMPLE 46: Isolation of cDNA clones Encoding Human PRO1115

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, designated Incyte EST cluster sequence no. 165008. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55726.

In light of an observed sequence homology between the DNA55726 consensus sequence and an EST sequence encompassed within the Merck EST clone no. R75784, the Merck EST clone R75784 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 111 and is herein designated as DNA56868-1478.

The full length clone shown in Figure 110 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 189-191 and ending at the stop codon found at nucleotide positions 1524-1526 (Figure 110; SEQ ID NO:176). The predicted polypeptide precursor (Figure 111, SEQ ID NO:177) is 445 amino acids long. PRO1115 has a calculated molecular weight of approximately 50,533 Daltons and an estimated pI of approximately 8.26. Additional features include a signal peptide at about amino acids 1-20; potential N-glycosylation sites at about amino acids 204-207, 295-298, and 313-316; and putative transmembrane domains at about amino acids 35-54, 75-97, 126-146, 185-204, 333-350, and 353-371.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 111 (SEQ ID NO:177), evidenced some amino acid sequence identity between the PRO1115 amino acid sequence and the following Dayhoff sequences: AF053947_79, S73698, CEC47A10_4, CCOMTNDSSG_1, HS4LMP2AC_1, LMP2_EBV, PA24_MOUSE, HCU33331_7, P-W05508, and AF002273_1.

- 5 Clone DNA56868-1478 was deposited with the ATCC on June 23, 1998 and is assigned ATCC deposit no. 203024..

EXAMPLE 47: Isolation of cDNA clones Encoding Human PRO1277

- 10 A consensus DNA sequence was assembled relative to other ESTs using repeated cycles of BLAST and the program "phrap" as described in Example 1 above. One or more of the ESTs from the assembly was derived from diseased coronary artery tissue. The consensus sequence obtained is designated herein as "DNA49434".

- 15 In light of an observed sequence homology between the DNA49434 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3042605, the Incyte EST clone 3042605 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 112 (SEQ ID NO:178).

- 20 Clone DNA56869-1545 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 188-190, and an apparent stop codon at nucleotide positions 2222-2224 (Figure 112). The predicted polypeptide precursor is 678 amino acids long (Figure 113). The full-length PRO1277 protein shown in Figure 113 has an estimated molecular weight of about 73,930 daltons and a pI of about 9.48. Additional features include a signal peptide at about amino acids 1-26; a transmembrane domain at about amino acids 181-200, and potential N-glycosylation sites at about amino acids 390-393 and 520-523.

- 25 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 113 (SEQ ID NO:179), revealed significant homology between the PRO1277 amino acid sequence and Dayhoff sequence no AF012252_1. Homology was also found between the PRO1277 amino acid sequence and the following Dayhoff sequences: AF006740_1, CA36_HUMAN, HSU1_1, HUMCOL7A1X_1, CA17_HUMAN, MMZ78163_1, CAMA_CHICK, HSU69263_1, YNX3_CAEEL, and MMRNAM3_1.

- 30 Clone DNA56869-1545 has been deposited with ATCC and is assigned ATCC deposit no. 203161.

EXAMPLE 48: Isolation of cDNA Clones Encoding Human PRO1135

- 35 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA52767. Based on the DNA52767 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1135.

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with PCR primer pairs prepared based upon the DNA52767 sequence. A positive library was then used to isolate clones encoding the PRO1135 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human coronary artery smooth muscle tissue (LIB309). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1135 [herein designated as DNA56870-1492] (SEQ ID NO:180) and the derived protein sequence for PRO1135.

The entire nucleotide sequence of DNA56870-1492 is shown in Figure 114 (SEQ ID NO:180). Clone DNA56870-1492 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 62-64 and ending at the stop codon at nucleotide positions 1685-1687 (Figure 114). The predicted polypeptide precursor is 541 amino acids long (Figure 115). The full-length PRO1135 protein shown in Figure 115 has an estimated molecular weight of about 60,335 daltons and a pI of about 5.26. Analysis of the full-length PRO1135 sequence shown in Figure 115 (SEQ ID NO:181) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, potential N-glycosylation sites from about amino acid 53 to about amino acid 56, from about amino acid 75 to about amino acid 78, from about amino acid 252 to about amino acid 255 and from about amino acid 413 to about amino acid 416 and an amino acid block having homology to glycosyl hydrolase family 35 proteins from about amino acid 399 to about amino acid 414. Clone DNA56870-1492 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209925.

Analysis of the amino acid sequence of the full-length PRO1135 polypeptide suggests that it possesses significant sequence similarity to the alpha 1,2-mannosidase protein, thereby indicating that PRO1135 may be a novel mannosidase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO1135 amino acid sequence and the following Dayhoff sequences, DMC86E4_5, D86967_1, SPAC23A1_4, YH04_YEAST, B54408, SS MAN9MAN_1, CEZC410_4, S61631 and MSU14190_1.

EXAMPLE 49: Isolation of cDNA Clones Encoding Human PRO1114

A cDNA sequence isolated in the amylase screen described in Example 2 above was found, by the WU-BLAST-2 sequence alignment computer program, to have certain sequence identity to other known interferon receptors. This cDNA sequence is herein designated DNA48466 and is shown in Figure 118 (SEQ ID NO:184).

Based on the sequence identity, probes were generated from the sequence of the DNA48466 molecule and used to screen a human breast carcinoma library (LIB135) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes

et al., Science, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

The oligonucleotide probes employed were as follows:

forward PCR primer 5'-AGGCTTCGCTGCGACTAGACCTC-3' (SEQ ID NO:185)

reverse PCR primer 5'-CCAGGTCGGGTAAGGATGGTTGAG-3' (SEQ ID NO:186)

hybridization probe

5 5'-TTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGC-3' (SEQ ID NO:187)

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 250-252, and a stop signal at nucleotide positions 1183-1185 (Figure 116, SEQ ID NO:182). The predicted polypeptide precursor is 311 amino acids long, has a calculated molecular weight of approximately 35,076 daltons and an estimated pI of approximately 5.04. Analysis of the full-length PRO1114 interferon receptor sequence shown in Figure 117 (SEQ ID NO:183) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 29, a transmembrane domain from about amino acid 230 to about amino acid 255, potential N-glycosylation sites from about amino acid 40 to about amino acid 43 and from about amino acid 134 to about amino acid 137, an amino acid sequence block having homology to tissue factor proteins from about amino acid 92 to about amino acid 119 and an amino acid sequence block having homology to integrin alpha chain proteins from about amino acid 232 to about amino acid 262. Clone DNA57033-1403 has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209905.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 117 (SEQ ID NO:183), evidenced significant homology between the PRO1114 interferon receptor amino acid sequence and the following Dayhoff sequences: G01418, INR1_MOUSE, P_R71035, INGS_HUMAN, A26595_1, A26593_1, I56215 and TF_HUMAN.

EXAMPLE 50: Isolation of cDNA Clones Encoding Human PRO828

A consensus DNA sequence was identified using the method described in Example 1 above. This consensus sequence is herein designated DNA35717. Based on the DNA35717 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO828.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCAGGACTTCTACGACTTCAAGGC-3' (SEQ ID NO:190); and

30 reverse PCR primer 5'-AGTCTGGGCCAGTACTTGAAGGC-3' (SEQ ID NO:191).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35717 sequence which had the following nucleotide sequence:

hybridization probe

5'-CAACATCCGGGGCAAACCTGGTGTGCTGGAGAAGTACCGCGGATCGGTGT-3' (SEQ ID NO:192)

35 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO828 gene using the probe oligonucleotide and one of the PCR primers. RNA

for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO828 [herein designated as DNA57037-1444] (SEQ ID NO:188) and the derived protein sequence for PRO828.

The entire nucleotide sequence of DNA57037-1444 is shown in Figure 119 (SEQ ID NO:188). Clone DNA57037-1444 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 34-36 and ending at the stop codon at nucleotide positions 595-597 (Figure 119). The predicted polypeptide precursor is 187 amino acids long (Figure 120). The full-length PRO828 protein shown in Figure 120 has an estimated molecular weight of about 20,996 daltons and a pI of about 8.62. Analysis of the full-length PRO828 sequence shown in Figure 120 (SEQ ID NO:189) evidences the presence of the following: a signal peptide at about amino acids 1- 21; sequences identity to glutathione peroxidases signature 2 at about amino acids 82-89; sequence identity to glutathione peroxidases selenocysteine proteins at about amino acids 35-60, 63-100, 107-134, and 138-159. Clone DNA57037-1444 has been deposited with ATCC on May 27, 1998, and is assigned ATCC deposit no. 209903.

Analysis of the amino acid sequence of the full-length PRO828 polypeptide suggests that it possesses significant sequence similarity to glutathione peroxidases, thereby indicating that PRO828 may be a novel peroxidase enzyme. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO828 amino acid sequence and the following Dayhoff sequences: AF053311_1, CELT09A12_2, AC004151_3, BTUE_ECOLI, CER05H10_3, P_P80918, PWU88907_1, and P_W22308.

EXAMPLE 51: Isolation of cDNA clones Encoding Human PRO1009

A cDNA clone (DNA57129-1413) encoding a native human PRO1009 polypeptide was identified by the use of a yeast screen, in a human SK-Lu-1 adenocarcinoma cell line cDNA library that preferentially represents the 5' ends of the primary cDNA clones. First SEQ ID NO:195 (Figure 123) was identified, which was extended by alignments to other EST sequences to form a consensus sequence. Oligonucleotide probes based upon the consensus sequence were synthesized and used to screen the cDNA library which gave rise to the full-length DNA57129-1413 clone.

The full length DNA57129-1413 clone shown in Figure 121 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 41-43 and ending at the stop codon found at nucleotide positions 1886-1888 (Figure 121; SEQ ID NO:193). The predicted polypeptide precursor (Figure 122, SEQ ID NO:194) is 615 amino acids long. Figure 122 also shows the approximate locations of the signal sequence, transmembrane domains, myristoylation sites, a glycosylation site and an AMP-binding domain. PRO1009 has a calculated molecular weight of approximately 68,125 daltons and an estimated pI of approximately 7.82. Clone DNA57129-1413 has been deposited with ATCC and is assigned ATCC deposit no. 209977. It is understood that the deposited clone has the actual and correct sequence and that the representations herein may have minor, normal sequencing errors.

Based on a WU-BLAST-2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1009 shows amino acid sequence identity to at least the following proteins which were designated in a Dayhoff database as follows: F69893, CEF28F8_2, BSY13917_7, BSY13917_7, D69187, D69649, XCRPFB_1, E64928, YDID_ECOLI, BNACSF8_1 and RPU75363_2.

5 **EXAMPLE 52: Isolation of cDNA Clones Encoding Human PRO1007**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated as DNA40671.

10 In light of an observed sequence homology between the DNA40671 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T70513, the Merck EST clone T70513 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 124.

The entire nucleotide sequence of DNA57690-1374 is shown in Figure 124 (SEQ ID NO:196). Clone DNA57690-1374 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 16-18 and ending at the stop codon at nucleotide positions 1054-1056 (Figure 124). The predicted polypeptide precursor is 346 amino acids long (Figure 125). The full-length PRO1007 protein shown in Figure 125 has an estimated molecular weight of about 35,971 daltons and a pI of about 8.17. Clone DNA57690-1374 has been deposited with the ATCC on June 9, 1998. Regarding the sequence, it is understood that the deposited clone contains the actual sequence, and the sequences provided herein are based on known sequencing techniques. The representative figures herein show the representative numbering.

20 Analysis of the amino acid sequence of the full-length PRO1007 polypeptide suggests that portions of it possess sequence identity to MAGPIAP, thereby indicating that PRO1007 may be a novel member of the family to which MAGPIAP belongs.

Still analyzing the amino acid sequence of SEQ ID NO:197, the putative signal peptide is at about amino acids 1-30 of SEQ ID NO:197. The transmembrane domain is at amino acids 325-346 of SEQ ID NO:197. N-glycosylation sites are at about amino acids 118-121, 129-132, 163-166, 176-179, 183-186 and 227-230 of SEQ ID NO:197. Ly-6/u-Par domain protein homology is at about amino acids 17-36 and 209-222 of SEQ ID NO:197. The corresponding nucleotides of the amino acids presented herein can be routinely determined given the sequences provided herein.

30 **EXAMPLE 53: Isolation of cDNA clones Encoding Human PRO1056**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as 6425. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a

consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55736.

In light of an observed sequence homology between the DNA55736 consensus sequence and an EST sequence encompassed within the Merck EST clone no. R88049, the Merck EST clone R88049 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

5 The sequence of this cDNA insert is shown in Figure 126 and is herein designated as DNA57693-1424.

Clone DNA57693-1424 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 56-58 and ending at the stop codon at nucleotide positions 416-418 (Figure 126). The predicted polypeptide precursor is 120 amino acids long (Figure 127). The full-length PRO1056 protein shown in Figure 127 has an estimated molecular weight of about 13,345 daltons and a pI of about 5.18. Analysis of
10 the full-length PRO1056 sequence shown in Figure 127 (SEQ ID NO:199) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 18, a transmembrane domain from about amino acid 39 to about amino acid 58, a potential N-glycosylation site from about amino acid 86 to about amino acid 89, protein kinase C phosphorylation sites from about amino acid 36 to about amino acid 38 and from about amino acid 58 to about amino acid 60, a tyrosine kinase phosphorylation site from about amino acid 25 to about
15 amino acid 32 and an amino acid sequence block having homology to channel forming colicin proteins from about amino acid 24 to about amino acid 56. Clone DNA57693-1424 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203008.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 127 (SEQ ID NO:199), evidenced significant
20 homology between the PRO1056 amino acid sequence and the following Dayhoff sequences: PLM_HUMAN, A40533, ATNG_HUMAN, A55571, ATNG_SHEEP, S31524, GEN13025, RIC_MOUSE, A48678 and A10871_1.

EXAMPLE 54: Isolation of cDNA clones Encoding Human PRO826

25 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 47283. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul
30 et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56000.

In light of an observed sequence homology between the DNA56000 consensus sequence and an EST
35 sequence encompassed within the Merck EST clone no. W69233, the Merck EST clone W69233 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 128 and is herein designated as DNA57694-1341.

Clone DNA57694-1341 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 13-15 and ending at the stop codon at nucleotide positions 310-312 (Figure 128). The predicted polypeptide precursor is 99 amino acids long (Figure 129). The full-length PRO826 protein shown in Figure 129 has an estimated molecular weight of about 11,050 daltons and a pI of about 7.47. Analysis of the full-length PRO826 sequence shown in Figure 129 (SEQ ID NO:201) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 22, potential N-myristoylation sites from about amino acid 22 to about amino acid 27 and from about amino acid 90 to about amino acid 95 and an amino acid sequence block having homology to peroxidase from about amino acid 16 to about amino acid 48. Clone DNA57694-1341 has been deposited with ATCC on June 22, 1998 and is assigned ATCC deposit no. 203017.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 129 (SEQ ID NO:201), evidenced significant homology between the PRO826 amino acid sequence and the following Dayhoff sequences: CCU12315_1, SCU96108_6, CELF39F10_4 and HELT_HELHO.

EXAMPLE 55: Isolation of cDNA clones Encoding Human PRO819

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 49605. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56015.

In light of an observed sequence homology between the DNA56015 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H65785, the Merck EST clone H65785 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 130 and is herein designated as DNA57695-1340.

Clone DNA57695-1340 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 46-48 and ending at the stop codon at nucleotide positions 202-204 (Figure 130). The predicted polypeptide precursor is 52 amino acids long (Figure 131). The full-length PRO819 protein shown in Figure 131 has an estimated molecular weight of about 5,216 daltons and a pI of about 4.67. Analysis of the full-length PRO819 sequence shown in Figure 131 (SEQ ID NO:203) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a potential N-myristoylation site from about amino acid 2 to about amino acid 7 and a region having homology to immunoglobulin light chain from about amino acid 5 to about amino acid 33. Clone DNA57695-1340 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203006.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 131 (SEQ ID NO:203), evidenced significant homology between the PRO819 amino acid sequence and the following Dayhoff sequences: HSU03899_1, HUMIGLITEB_1, VG28_HSVSA, AF031522_1, PAD1_YEAST and AF045484_1.

5 EXAMPLE 56: Isolation of cDNA Clones Encoding Human PRO1006

An initial candidate sequence from Incyte cluster sequence no. 45748 was identified using the signal algorithm process described in Example 3 above. This sequence was then aligned with a variety of public and Incyte EST sequences and a consensus sequence designated herein as DNA56036 was derived therefrom.

10 In light of an observed sequence homology between the DNA56036 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 489737, the Merck EST clone 489737 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 132.

The entire nucleotide sequence of DNA57699-1412 is shown in Figure 132 (SEQ ID NO:204). Clone DNA57699-1412 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 28-30 and ending at the stop codon at nucleotide positions 1204-1206 (Figure 132). The predicted polypeptide precursor is 392 amino acids long (Figure 133). The full-length PRO1006 protein shown in Figure 133 has an estimated molecular weight of about 46,189 daltons and a pI of about 9.04. Clone DNA57699-1412 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

20 Analyzing the amino acid sequence of SEQ ID NO:205, the putative signal peptide is at about amino acids 1-23 of SEQ ID NO:205. The N-glycosylation sites are at about amino acids 40-43, 53-56, 204-207 and 373-376 of SEQ ID NO:205. An N-myristoylation site is at about amino acids 273-278 of SEQ ID NO:205.

The corresponding nucleotides of these amino acid regions and others can be routinely determined given the sequences provided herein.

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EXAMPLE 57: Isolation of cDNA Clones Encoding Human PRO1112

Use of the signal sequence algorithm described in Example 3 above allowed identification of a specific EST cluster sequence. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56018.

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In light of an observed sequence homology between the DNA56018 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA223546, the Merck EST clone AA223546 was

purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 134 and is herein designated as DNA57702-1476.

The entire nucleotide sequence of DNA57702-1476 is shown in Figure 134 (SEQ ID NO:206). Clone DNA57702-1476 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 20-22 and ending at the stop codon at nucleotide positions 806-808 of SEQ ID NO:206 (Figure 134).

5 The predicted polypeptide precursor is 262 amino acids long (Figure 135). The full-length PRO1112 protein shown in Figure 135 has an estimated molecular weight of about 29,379 daltons and a pI of about 8.93. Figure 135 also shows the approximate locations of the signal peptide and transmembrane domains. Clone DNA57702-1476 has been deposited with the ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

10 Analysis of the amino acid sequence of the full-length PRO1112 polypeptide suggests that it possesses some sequence similarity to other proteins. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO1112 amino acid sequence and at least the following Dayhoff sequences, MTY20B11_13 (a mycobacterium tuberculosis peptide), F64471, AE000690_6, XLU16364_1, E43259 (H⁺-transporting ATP synthase) and PIGSLADRXE_1 (MHC class II
15 histocompatibility antigen).

EXAMPLE 58: Isolation of cDNA clones Encoding Human PRO1074

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence (Incyte cluster sequence No. 42586). This cluster sequence was then compared to
20 a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQTM, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus
25 DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56251.

In light of an observed sequence homology between the DNA56251 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA081912, the Merck EST clone AA081912 was
30 purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 136 and is the full-length DNA sequence for PRO1074. Clone DNA57704-1452 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209953.

The entire nucleotide sequence of DNA57704-1452 is shown in Figure 136 (SEQ ID NO:208). Clone DNA57704-1452 contains a single open reading frame with an apparent translational initiation site at nucleotide
35 positions 322-324 and ending at the stop codon at nucleotide positions 1315-1317 (Figure 136). The predicted polypeptide precursor is 331 amino acids long (Figure 137). The full-length PRO1074 protein shown in Figure 137 has an estimated molecular weight of about 39,512 Daltons and a pI of about 8.03. Analysis of the full-

length PRO1074 sequence shown in Figure 137 (SEQ ID NO:209) evidences the presence of the following features: a transmembrane domain at about amino acids 20 to 39; potential N-glycosylation sites at about amino acids 72 to 75, 154 to 157, 198 to 201, 212 to 215, and 326 to 329; a glycosaminoglycan attachment site at about amino acids 239 to 242, and a Ly-6/u-PAR domain at about amino acids 23 to 36.

Analysis of the amino acid sequence of the full-length PRO1074 polypeptide suggests that it possesses significant sequence similarity to beta 1,3-galactosyltransferase, thereby indicating that PRO1074 may be a novel member of the galactosyltransferase family of proteins. Analysis of the amino acid sequence of the full-length PRO1074 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1074 amino acid sequence and the following Dayhoff sequences: AF029792_1, P_R57433, DMU41449_1, AC000348_14, P_R47479, CET09F5_2, CEF14B6_4, CET15D6_5, CEC54C8_4, and CEE03H4_10.

Clone DNA57704-1452 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209953.

EXAMPLE 59: Isolation of cDNA clones Encoding Human PRO1005

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, Incyte cluster sequence no. 49243. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56380.

In light of an observed sequence homology between the DNA56380 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA256657, the Merck EST clone AA256657 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 138 and is herein designated as DNA57708-1411.

The full length clone shown in Figure 138 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 30-32 and ending at the stop codon found at nucleotide positions 585-587 (Figure 138; SEQ ID NO:210). The predicted polypeptide precursor (Figure 139, SEQ ID NO:211) is 185 amino acids long. PRO1005 has a calculated molecular weight of approximately 20,331 daltons and an estimated pI of approximately 5.85. Clone DNA57708-1411 was deposited with the ATCC June 23, 1998, and is assigned ATCC deposit no. 203021.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 139 (SEQ ID NO:211), evidenced some homology between the PRO1005 amino acid sequence and the following Dayhoff sequences: DDU07187_1, DDU87912_1, CELD1007_14, A42239, DDU42597_1, CYAG_DICD1, S50452, MRKC_KLEPN, P-R41998,

and XYNA_RUMFL.

EXAMPLE 60: Isolation of cDNA clones Encoding Human PRO1073

An initial DNA sequence referred to herein as DNA55938 and shown in Figure 142 (SEQ ID NO:214) was identified using a yeast screen, in a human SK-Lu-1 adenocarcinoma cell line cDNA library that preferentially represents the 5' ends of the primary cDNA clones. DNA55938 was then compared to ESTs from public databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)]. The ESTs were clustered and assembled into a consensus DNA sequence using the computer program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained is designated herein as DNA56411.

In light of an observed sequence homology between the DNA56411 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H86027, the Merck EST clone H86027 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 140.

The full length DNA57710-1451 clone shown in Figure 140 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 345-347 and ending at the stop codon found at nucleotide positions 1242-1244 (Figure 140; SEQ ID NO:212). The predicted polypeptide precursor (Figure 141, SEQ ID NO:213) is 299 amino acids long. PRO1073 has a calculated molecular weight of approximately 34,689 daltons and an estimated pI of approximately 11.49. The PRO1073 polypeptide has the following additional features: a signal peptide at about amino acids 1-31, sequence identity to bZIP transcription factor basic domain signature at about amino acids, a potential N-glycosylation site at about amino acids 2-5, and sequence identity with protamine P1 proteins at about amino acids 158-183.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 141 (SEQ ID NO:213), revealed some sequence identity between the PRO1073 amino acid sequence and the following Dayhoff sequences: MMU37351_1, ATAC00250510T9J22.10, S59043, ENXNUPR_1, B47328, SR55_DROME, S26650, SON_HUMAN, VIT2_CHICK, and XLC4SRPRT_1.

Clone DNA57710-1451 was deposited with the ATCC on July 1, 1998 and is assigned ATCC deposit no. 203048.

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EXAMPLE 61: Isolation of cDNA clones Encoding Human PRO1152

A cDNA clone (DNA57711-1501) encoding a native human PRO1152 polypeptide was identified by employing a yeast screen, in a human infant brain cDNA library that preferentially represents the 5' ends of the primary cDNA clones. Specifically, a yeast screen was employed to identify a cDNA designated herein as DNA55807 (SEQ ID NO:217; see Figure 145).

In light of an observed sequence homology between the DNA55807 sequence and an EST sequence encompassed within the Merck EST clone no. R56756, the Merck EST clone R56756 was purchased and the

cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 143.

The full-length DNA57711-1501 clone shown in Figure 143 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon at nucleotide positions 1495-1497 (Figure 143). The predicted polypeptide precursor is 479 amino acids long (Figure 144).

- 5 The full-length PRO1152 protein shown in Figure 144 has an estimated molecular weight of about 53,602 daltons and a pI of about 8.82. Analysis of the full-length PRO1152 sequence shown in Figure 144 (SEQ ID NO:216) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, transmembrane domains from about amino acid 133 to about amino acid 155, from about amino acid 168 to about amino acid 187, from about amino acid 229 to about amino acid 247, from about amino acid 264 to about amino acid 285, from about amino acid 309 to about amino acid 330, from about amino acid 371 to about amino acid 390 and from about amino acid 441 to about amino acid 464, potential N-glycosylation sites from about amino acid 34 to about amino acid 37 and from about amino acid 387 to about amino acid 390 and an amino acid sequence block having homology to a respiratory-chain NADH dehydrogenase subunit from about amino acid 243 to about amino acid 287. Clone DNA57711-1501 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203047.

- 15 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 144 (SEQ ID NO:216), evidenced significant homology between the PRO1152 amino acid sequence and the following Dayhoff sequences: AF052239_1, SYNN9CGA_1, SFCYTB2_1, GEN12507, P_R11769, MTV025_109, C61168, S43171, P_P61689 and P_P61696.

EXAMPLE 62: Isolation of cDNA clones Encoding Human PRO1136

- Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 109142. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56039.

- In light of an observed sequence homology between the DNA56039 consensus sequence and an EST sequence encompassed within the Merck EST clone no. HSC1NF011, the Merck EST clone HSC1NF011 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 146 and is herein designated as DNA57827-1493.

Clone DNA57827-1493 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 216-218 and ending at the stop codon at nucleotide positions 2112-2114 (Figure 146).

The predicted polypeptide precursor is 632 amino acids long (Figure 147). The full-length PRO1136 protein shown in Figure 147 has an estimated molecular weight of about 69,643 daltons and a pI of about 8.5. Analysis of the full-length PRO1136 sequence shown in Figure 147 (SEQ ID NO:219) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 15 and potential N-glycosylation sites from about amino acid 108 to about amino acid 11, from about amino acid 157 to about amino acid 160, from about amino acid 289 to about amino acid 292 and from about amino acid 384 to about amino acid 387. Clone DNA57827-1493 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203045.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 147 (SEQ ID NO:219), evidenced significant homology between the PRO1136 amino acid sequence and the following Dayhoff sequences: AF034746_1, AF034745_1, MMAF000168_19, HSMUPP1_1, AF060539_1, SP97_RAT, I38757, MMU93309_1, CEK01A6_4 and HSA224747_1.

EXAMPLE 63: Isolation of cDNA clones Encoding Human PRO813

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence (Incyte EST cluster sequence no. 45501. The Incyte EST cluster sequence no. 45501 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56400.

In light of an observed sequence homology between the DNA56400 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T90592, the Merck EST clone T90592 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 148 and is herein designated DNA57834-1339.

The full length clone shown in Figure 148 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 109-111 and ending at the stop codon found at nucleotide positions 637-639 (Figure 149; SEQ ID NO:221). The predicted polypeptide precursor is 176 amino acids long, has a calculated molecular weight of approximately 19,616 daltons and an estimated pI of approximately 7.11. Analysis of the full-length PRO813 sequence shown in Figure 149 (SEQ ID NO:221) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 26 and potential N-myristoylation sites from about amino acid 48 to about amino acid 53, from about amino acid 153 to about amino acid 158, from about amino acid 156 to about amino acid 161 and from about amino acid 167 to about amino acid 172. Clone DNA57834-1339 has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209954.

Analysis of the amino acid sequence of the full-length PRO813 polypeptide suggests that it possesses sequence similarity to the pulmonary surfactant-associated protein C. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO813 amino acid sequence and the following Dayhoff sequences, P_{SPC_MUSVI}, P_{P92071}, G02964, P_{R65489}, P_{P82977}, P_{R84555}, S55542, MUSIGHAJ_1 and PH1158.

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EXAMPLE 64: Isolation of cDNA Clones Encoding Human PRO809

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence. The Incyte EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56418.

In light of an observed sequence homology between the DNA56418 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H74302, the Merck EST clone H74302 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 150 and is herein designated DNA57836-1338.

The entire nucleotide sequence of DNA57836-1338 is shown in Figure 150 (SEQ ID NO:222). Clone DNA57836-1338 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 63-65 and ending at the stop codon at nucleotide positions 858-860 of SEQ ID NO:222 (Figure 150). The predicted polypeptide precursor is 265 amino acids long (Figure 151). The full-length PRO809 protein shown in Figure 151 has an estimated molecular weight of about 29,061 daltons and a pI of about 9.18. Figure 151 further shows the approximate positions of the signal peptide and N-glycosylation sites. The corresponding nucleotides can be determined by referencing Figure 150. Clone DNA57836-1338 has been deposited with ATCC on June 23, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO809 polypeptide suggests that it possesses some sequence similarity to the heparin sulfate proteoglycan and to endothelial cell adhesion molecule-1. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO809 amino acid sequence and the following Dayhoff sequences, P_{GBM_MOUSE}, D82082_1 and PW14158.

EXAMPLE 65: Isolation of cDNA Clones Encoding Human PRO791

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence. The Incyte EST cluster sequence was then compared to a variety of expressed

sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56429.

In light of an observed sequence homology between the DNA56429 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 36367, the Merck EST clone 36367 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 152 and is herein designated DNA57838-1337.

The entire nucleotide sequence of DNA57838-1337 is shown in Figure 152 (SEQ ID NO:224). Clone DNA57838-1337 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 9-11 and ending at the stop codon at nucleotide positions 747-749 of SEQ ID NO:224 (Figure 152). The predicted polypeptide precursor is 246 amino acids long (Figure 153). The full-length PRO791 protein shown in Figure 153 has an estimated molecular weight of about 27,368 daltons and a pI of about 7.45. Figure 153 also shows the approximate locations of the signal peptide, the transmembrane domain, N-glycosylation sites and a region conserved in extracellular proteins. The corresponding nucleotides of one embodiment provided herein can be identified by referencing Figure 152. Clone DNA57838-1337 has been deposited with ATCC on June 23, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO791 polypeptide suggests that it has sequence similarity with MHC-I antigens, thereby indicating that PRO791 may be related to MHC-I antigens. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO791 amino acid sequence and the following Dayhoff sequences, AF034346_1, MMQ1K5_1 and HFE_HUMAN.

EXAMPLE 66: Isolation of cDNA clones Encoding Human PRO1004

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence, Incyte cluster sequence No. 73681. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated as DNA56516.

In light of an observed sequence homology between the DNA56516 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H43837, the Merck EST clone H43837 was purchased

and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 154.

The full length clone shown in Figure 154 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 119-121 and ending at the stop codon at nucleotide positions 464-466 (Figure 154; SEQ ID NO:226). The predicted polypeptide precursor is 115 amino acids long (Figure 155; SEQ ID NO:227). The full-length PRO1004 protein shown in Figure 155 has an estimated molecular weight of about 13,649 daltons and a pI of about 9.58. Analysis of the full-length PRO1004 sequence shown in Figure 155 (SEQ ID NO:227) evidences the presence of the following features: a signal peptide at about amino acids 1-24, a microbodies C-terminal targeting signal at about amino acids 113-115, a potential N-glycosylation site at about amino acids 71-74, and a domain having sequence identity with dihydrofolate reductase proteins at about amino acids 22-48.

Analysis of the amino acid sequence of the full-length PRO1004 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1004 amino acid sequence and the following Dayhoff sequences: CELR02D3_7, LEC1_MOUSE, AF006691_3, SSZ97390_1, SSZ97395_1, and SSZ97400_1.

Clone DNA57844-1410 was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no. 203010.

EXAMPLE 67: Isolation of cDNA clones Encoding Human PRO1111

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which had homology to insulin-like growth factor binding protein.

RNA for construction of cDNA libraries was isolated from human fetal brain. The cDNA libraries used to isolate the cDNA clones encoding human PRO1111 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

The human fetal brain cDNA libraries (prepared as described above), were screened by hybridization with a synthetic oligonucleotide probe based upon the Incyte EST sequence described above:

5'-CCACCACCTGGAGGTCCTGCAGTTGGGCAGGAAGTCCATCCGGCAGATTG-3' (SEQ ID NO:251).

An identified cDNA clone was sequenced in entirety. The entire nucleotide sequence of PRO1111 is shown in Figure 156 (SEQ ID NO:228). Clone DNA58721-1475 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 57-59 and a stop codon at nucleotide positions 2016-2018 (Figure 156; SEQ ID NO:228). The predicted polypeptide precursor is 653 amino acids long (Figure 157).

The transmembrane domains are at positions 21-40 (type II) and 528-548. Clone DNA58721-1475 has been deposited with ATCC and is assigned ATCC deposit no. 203110. The full-length PRO1111 protein shown in Figure 157 has an estimated molecular weight of about 72,717 daltons and a pI of about 6.99.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 157 (SEQ ID NO:229), revealed some sequence identity between the PRO1111 amino acid sequence and the following Dayhoff sequences: A58532, D86983_1, RNPLGPV_1, PGS2_HUMAN, AF038127_1, ALS_MOUSE, GPV_HUMAN, PGS2_BOVIN, ALS_PAPPA and I47020.

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EXAMPLE 68: Isolation of cDNA clones Encoding Human PRO1344

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA33790. Based on the DNA33790 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1344.

PCR primers (forward and reverse) were synthesized:
forward PCR primer 5'-AGGTTCGTGATGGAGACAACCGCG-3' (SEQ ID NO:232)
reverse PCR primer 5'-TGTC AAGGACGCACTGCCGTCATG-3' (SEQ ID NO:233)

15 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA33790 sequence which had the following nucleotide sequence

hybridization probe

5'-TGGCCAGATCATCAAGCGTGTCTGTGGCAACGAGCGGCCAGCTCCTATCC-3' (SEQ ID NO:234)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1344 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1344 (designated herein as DNA58723-1588 [Figure 158, SEQ ID NO:230]); and the derived protein sequence for PRO1344.

The entire nucleotide sequence of DNA58723-1588 is shown in Figure 158 (SEQ ID NO:230). Clone DNA58723-1588 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 26-28 and ending at the stop codon at nucleotide positions 2186-2188 (Figure 158). The predicted polypeptide precursor is 720 amino acids long (Figure 159). The full-length PRO1344 protein shown in Figure 159 has an estimated molecular weight of about 80,199 daltons and a pI of about 7.77. Analysis of the full-length PRO1344 sequence shown in Figure 159 (SEQ ID NO:231) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, an EGF-like domain cysteine protein signature sequence from about amino acid 260 to about amino acid 271, potential N-glycosylation sites from about amino acid 96 to about amino acid 99, from about amino acid 279 to about amino acid 282, from about amino acid 316 to about amino acid 319, from about amino acid 451 to about amino acid 454 and from about amino acid 614 to about amino acid 617, an amino acid sequence block having homology to serine proteases, trypsin family from about amino acid 489 to about amino acid 505 and a CUB domain protein profile sequence from about amino

acid 150 to about amino acid 166. Clone DNA58723-1588 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203133.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 159 (SEQ ID NO:231), evidenced significant homology between the PRO1344 amino acid sequence and the following Dayhoff sequences: S77063_1, CRAR_MOUSE, P_R74775, P_P90070, P_R09217, P_P70475, HSBMP16_1 and U50330_1.

EXAMPLE 69: Isolation of cDNA clones Encoding Human PRO1109

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA52642. The consensus DNA sequence was obtained by extending using repeated cycles of BLAST and phrap a previously obtained consensus sequence as far as possible using the sources of EST sequences discussed above. Based on the DNA52642 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1109.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCTTACCTCAGAGGCCAGAGCAAGC-3' (SEQ ID NO:237)

reverse PCR primer 5'-GAGCTTCATCCGTTCTGCGTTCACC-3' (SEQ ID NO:238)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA52642 sequence which had the following nucleotide sequence

hybridization probe

5'-CAGGAATGTAAAGCTTTACAGAGGGTCGCCATCCTCGTTCCCCACC-3' (SEQ ID NO:239)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1109 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human SK-Lu-1 adenocarcinoma cell tissue (LIB247).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1109 (designated herein as DNA58737-1473 [Figure 160, SEQ ID NO:235]) and the derived protein sequence for PRO1109.

The entire nucleotide sequence of DNA58737-1473 is shown in Figure 160 (SEQ ID NO:235). Clone DNA58737-1473 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 119-120 and ending at the stop codon at nucleotide positions 1151-1153 (Figure 160). The predicted polypeptide precursor is 344 amino acids long (Figure 161). The full-length PRO1109 protein shown in Figure 161 has an estimated molecular weight of about 40,041 daltons and a pI of about 9.34. Analysis of the full-length PRO1109 sequence shown in Figure 161 (SEQ ID NO:236) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 27, potential N-glycosylation sites from about amino acid 4 to about amino acid 7, from about amino acid 220 to about amino acid 223 and from about amino acid 335 to about amino acid 338 and an amino acid sequence block having homology to xylose isomerase proteins from about amino acid 191 to about amino acid 201. Clone DNA58737-1473 has been deposited with ATCC

on August 18, 1998 and is assigned ATCC deposit no. 203136.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 161 (SEQ ID NO:236), evidenced significant homology between the PRO1109 amino acid sequence and the following Dayhoff sequences: HSUDPGAL_1, HSUDPB14_1, NALS_BOVIN, HSU10473_1, CEW02B12_11, YNJ4_CAEEL, AE000738_11, CET24D1_1, S48121 and CEGLY9_1.

EXAMPLE 70: Isolation of cDNA clones Encoding Human PRO1383

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA53961. Based on the DNA53961 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1383.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CATTCCTTACCCTGGACCCAGCTCC-3' (SEQ ID NO:242)

reverse PCR primer 5'-GAAAGGCCACAGCACATCTGGCAG-3' (SEQ ID NO:243)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA53961 sequence which had the following nucleotide sequence

hybridization probe

5'-CCACGACCCGAGCAACTTCCTCAAGACCGACTTGTCTCTACAGC-3' (SEQ ID NO:244)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1383 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1383 (designated herein as DNA58743-1609 [Figure 162, SEQ ID NO: 240]) and the derived protein sequence for PRO1383.

The entire nucleotide sequence of DNA58743-1609 is shown in Figure 162 (SEQ ID NO:240). Clone DNA58743-1609 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 122-124 and ending at the stop codon at nucleotide positions 1391-1393 (Figure 162). The predicted polypeptide precursor is 423 amino acids long (Figure 163). The full-length PRO1383 protein shown in Figure 163 has an estimated molecular weight of about 46,989 daltons and a pI of about 6.77. Analysis of the full-length PRO1383 sequence shown in Figure 163 (SEQ ID NO:241) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a transmembrane domain from about amino acid 339 to about amino acid 362, and potential N-glycosylation sites from about amino acid 34 to about amino acid 37, from about amino acid 58 to about amino acid 61, from about amino acid 142 to about amino acid 145, from about amino acid 197 to about amino acid 200, from about amino acid 300 to about amino acid 303 and from about amino acid 364 to about amino acid 367. Clone DNA58743-1609 has been deposited with ATCC on

August 25, 1998 and is assigned ATCC deposit no. 203154.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 163 (SEQ ID NO:241), evidenced significant homology between the PRO1383 amino acid sequence and the following Dayhoff sequences: NMB_HUMAN, QNR_COTJA, P_W38335, P115_CHICK, P_W38164, A45993_1, MMU70209_1, D83704_1 and P_W39176.

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EXAMPLE 71: Isolation of cDNA Clones Encoding Human PRO1003

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as 43055. This sequence was then compared to a variety of EST databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated consen01.

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In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2849382, the Incyte EST clone 2849382 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 164.

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The entire nucleotide sequence of DNA58846-1409 is shown in Figure 164 (SEQ ID NO:245). Clone DNA58846-1409 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 41-43 and ending at the stop codon at nucleotide positions 293-295 (Figure 164). The predicted polypeptide precursor is 84 amino acids long (Figure 165). The full-length PRO1003 protein shown in Figure 165 has an estimated molecular weight of about 9,408 daltons and a pI of about 9.28. Analysis of the full-length PRO1003 sequence shown in Figure 165 (SEQ ID NO:246) evidences the presence of a signal peptide at amino acids 1 to about 24, and a cAMP- and cGMP-dependent protein kinase phosphorylation site at about amino acids 58 to about 61. Analysis of the amino acid sequence of the full-length PRO1003 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1003 amino acid sequence and the following Dayhoff sequences: AOPCZA363_3, SRTX_ATREN, A48298, MHVJHMS_1, VGL2_CVMJH, DHDHTC2_2, CORT_RAT, TAL6_HUMAN, P_W14123, and DVUFI_2.

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EXAMPLE 72: Isolation of cDNA Clones Encoding Human PRO1108

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA53237.

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In light of an observed sequence homology between the DNA53237 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2379881, the Incyte EST clone 2379881 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 166 and is herein designated DNA58848-1472.

The entire nucleotide sequence of DNA58848-1472 is shown in Figure 166 (SEQ ID NO:247). Clone DNA58848-1472 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 77-79 and ending at the stop codon at nucleotide positions 1445-1447 (Figure 166). The predicted polypeptide precursor is 456 amino acids long (Figure 167). The full-length PRO1108 protein shown in Figure 167 has an estimated molecular weight of about 52,071 daltons and a pI of about 9.46. Analysis of the full-length PRO1108 sequence shown in Figure 167 (SEQ ID NO:248) evidences the presence of the following: type II transmembrane domains from about amino acid 22 to about amino acid 42, from about amino acid 156 to about amino acid 176, from about amino acid 180 to about amino acid 199 and from about amino acid 369 to about amino acid 388, potential N-glycosylation sites from about amino acid 247 to about amino acid 250, from about amino acid 327 to about amino acid 330, from about amino acid 328 to about amino acid 331 and from about amino acid 362 to about amino acid 365 and an amino acid block having homology to ER lumen protein retaining receptor protein from about amino acid 153 to about amino acid 190. Clone DNA58848-1472 has been deposited with ATCC on June 9, 1998 and is assigned ATCC deposit no. 209955.

Analysis of the amino acid sequence of the full-length PRO1108 polypeptide suggests that it possesses significant sequence similarity to the LPAAT protein, thereby indicating that PRO1108 may be a novel LPAAT homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO1108 amino acid sequence and the following Dayhoff sequences, AF015811_1, CER07E3_2, YL35_CAEEL, S73863, CEF59F4_4, P_W06422, MMU41736_1, MTV008_39, P_R99248 and Y67_BPT7.

EXAMPLE 73: Isolation of cDNA Clones Encoding Human PRO1137

The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Using this procedure, Incyte EST No. 3459449, also referred to herein as "DNA7108", was identified as an EST having a BLAST score of 70 or greater that did not encode a known protein.

A consensus DNA sequence was assembled relative to the DNA7108 sequence and other ESTs using repeated cycles of BLAST and the program "phrap" (Phil Green, Univ. of Washington, Seattle, WA). The consensus sequence obtained therefrom is referred to herein as DNA53952.

In light of an observed sequence homology between the DNA53952 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3663102, the Incyte EST clone 3663102 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 168.

The entire nucleotide sequence of DNA58849-1494 is shown in Figure 168 (SEQ ID NO:249). Clone DNA58849-1494 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 77-79 and ending at the stop codon at nucleotide positions 797-799 (Figure 168). The predicted polypeptide precursor is 240 amino acids long (Figure 169). The full-length PRO1137 protein shown in Figure 169 has an estimated molecular weight of about 26,064 daltons and a pI of about 8.65. Analysis of the full-length PRO1137 sequence shown in Figure 169 (SEQ ID NO:250) evidences the presence of a signal peptide at about amino acids 1 to 14 and a potential N-glycosylation site at about amino acids 101-105.

Analysis of the amino acid sequence of the full-length PRO1137 polypeptide suggests that it possesses significant sequence similarity to ribosyltransferase thereby indicating that PRO1137 may be a novel member of the ribosyltransferase family of proteins. Analysis of the amino acid sequence of the full-length PRO1137 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1137 amino acid sequence and the following Dayhoff sequences: MMART5_1, NARG_MOUSE, GEN11909, GEN13794, GEN14406, MMRNART62_1, and P_R41876.

EXAMPLE 74: Isolation of cDNA clones Encoding Human PRO1138

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence, Incyte cluster sequence no. 165212. This cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated as DNA54224. The assembly included a proprietary Genentech EST designated herein as DNA49140 (Figure 172; SEQ ID NO:254).

In light of an observed sequence homology between the DNA54224 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3836613, the Incyte EST clone 3836613 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 170 and is the full-length DNA sequence for PRO1138. Clone DNA58850-1495 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209956.

The entire nucleotide sequence of DNA58850-1495 is shown in Figure 170 (SEQ ID NO:252). Clone DNA58850-1495 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 38-40 and ending at the stop codon at nucleotide positions 1043-1045 (Figure 170). The predicted polypeptide precursor is 335 amino acids long (Figure 171). The full-length PRO1138 protein shown in Figure 171 has an estimated molecular weight of about 37,421 Daltons and a pI of about 6.36. Analysis of the full-length PRO1138 sequence shown in Figure 171 (SEQ ID NO:253) evidences the presence of the following features: a signal peptide at about amino acid 1 to about amino acid 22; a transmembrane domain at about amino

acids 224 to about 250; a leucine zipper pattern at about amino acids 229 to about 250; and potential N-glycosylation sites at about amino acids 98-101, 142-145, 148-151, 172-175, 176-179, 204-207, and 291-295.

Analysis of the amino acid sequence of the full-length PRO1138 polypeptide suggests that it possesses significant sequence similarity to the CD84, thereby indicating that PRO1138 may be a novel member of the Ig superfamily of polypeptides. More particularly, analysis of the amino acid sequence of the full-length PRO1138 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1138 amino acid sequence and the following Dayhoff sequences: HSU82988_1, HUMLY9_1, P_R97631, P_R97628, P_R97629, P_R97630, CD48_RAT, CD2_HUMAN, P_P93996, and HUMBGP_1.

Clone DNA58850-1495 was deposited with ATCC on June 9, 1998, and is assigned ATCC deposit no. 209956.

EXAMPLE 75: Isolation of cDNA clones Encoding Human PRO1054

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 66212. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55722.

In light of an observed sequence homology between the DNA55722 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 319751, the Incyte EST clone 319751 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 173 and is herein designated as DNA58853-1423.

Clone DNA58853-1423 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 46-48 and ending at the stop codon at nucleotide positions 586-588 (Figure 173). The predicted polypeptide precursor is 180 amino acids long (Figure 174). The full-length PRO1054 protein shown in Figure 174 has an estimated molecular weight of about 20,638 daltons and a pI of about 5.0. Analysis of the full-length PRO1054 sequence shown in Figure 174 (SEQ ID NO:256) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 18, a leucine zipper pattern from about amino acid 155 to about amino acid 176 and amino acid sequence blocks having homology to lipocalin proteins from about amino acid 27 to about amino acid 38 and from about amino acid 110 to about amino acid 120. Clone DNA58853-1423 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203016.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 174 (SEQ ID NO:256), evidenced significant homology between the PRO1054 amino acid sequence and the following Dayhoff sequences: MUP1_MOUSE, MUP6_MOUSE, MUP2_MOUSE, MUP8_MOUSE, MUP5_MOUSE, MUP4_MOUSE, S10124,

MUPM_MOUSE, MUP_RAT and ECU70823_1.

EXAMPLE 76: Isolation of cDNA clones Encoding Human PRO994

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 157555. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55728.

In light of an observed sequence homology between the DNA55728 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2860366, the Incyte EST clone 2860366 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 175 and is herein designated as DNA58855-1422.

Clone DNA58855-1422 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 31-33 and ending at the stop codon at nucleotide positions 718-720 (Figure 175). The predicted polypeptide precursor is 229 amino acids long (Figure 176). The full-length PRO994 protein shown in Figure 176 has an estimated molecular weight of about 25,109 daltons and a pI of about 6.83. Analysis of the full-length PRO994 sequence shown in Figure 176 (SEQ ID NO:258) evidences the presence of the following: transmembrane domains from about amino acid 10 to about amino acid 31, from about amino acid 50 to about amino acid 72, from about amino acid 87 to about amino acid 110 and from about amino acid 191 to about amino acid 213, potential N-glycosylation sites from about amino acid 80 to about amino acid 83, from about amino acid 132 to about amino acid 135, from about amino acid 148 to about amino acid 151 and from about amino acid 163 to about amino acid 166 and an amino acid block having homology to TNFR/NGFR cysteine-rich region proteins from about amino acid 4 to about amino acid 11. Clone DNA58855-1422 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203018.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 176 (SEQ ID NO:258), evidenced significant homology between the PRO994 amino acid sequence and the following Dayhoff sequences: AF027204_1, TAL6_HUMAN, ILT4_HUMAN, JC6205, MMU57570_1, S40363, ETU56093_1, S42858, P_R66849 and P_R74751.

EXAMPLE 77: Isolation of cDNA clones Encoding Human PRO812

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 170079. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank)

and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated as DNA55721.

In light of an observed sequence homology between the DNA55721 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 388964, the Incyte EST clone 388964 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 177 and is herein designated as DNA59205-1421.

Clone DNA59205-1421 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 55-57 and ending at the stop codon at nucleotide positions 304-306 (Figure 177). The predicted polypeptide precursor is 83 amino acids long (Figure 178). The full-length PRO812 protein shown in Figure 178 has an estimated molecular weight of about 9,201 daltons and a pI of about 9.3. Analysis of the full-length PRO812 sequence shown in Figure 178 (SEQ ID NO:260) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 15, a cAMP- and cGMP-dependent protein kinase phosphorylation site from about amino acid 73 to about amino acid 76 and protein kinase C phosphorylation sites from about amino acid 70 to about amino acid 72 and from about amino acid 76 to about amino acid 78. Clone DNA59205-1421 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203009.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 178 (SEQ ID NO:260), evidenced significant homology between the PRO812 amino acid sequence and the following Dayhoff sequences: P_W35802, P_W35803, PSC1_RAT, S68231, GEN13917, PSC2_RAT, CC10_HUMAN, UTER_RABIT, AF008595_1 and A56413.

EXAMPLE 78: Isolation of cDNA clones Encoding Human PRO1069

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence designated herein as 100727. This sequence was then compared to a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56001.

In light of an observed sequence homology between the DNA56001 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3533881, the Incyte EST clone 3533881 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 179 and is the full-length DNA sequence for PRO1069.

Clone DNA59211-1450 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209960.

The entire nucleotide sequence of DNA59211-1450 is shown in Figure 179 (SEQ ID NO:261). Clone DNA59211-1450 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 197-199 and ending at the stop codon at nucleotide positions 464-466. The predicted polypeptide precursor is 89 amino acids long (Figure 180). The full-length PRO1069 protein shown in Figure 180 has an estimated molecular weight of about 9,433 daltons and a pI of about 8.21. Analysis of the full-length PRO1069 sequence shown in Figure 180 (SEQ ID NO:262) evidences the presence of the following features: a signal peptide sequence at amino acid 1 to about 16; a transmembrane domain at about amino acids 36 to about 59; potential N-myristoylation sites at about amino acids 41-46, 45-50, and 84-89; and homology with extracellular proteins SCP/Tpx-1/Ag5/PR-1/Sc7 at about amino acids 54 to about 66.

Analysis of the amino acid sequence of the full-length PRO1069 polypeptide suggests that it possesses significant sequence similarity to CHIF, thereby indicating that PRO1069 may be a member of the CHIF family of polypeptides. More particularly, analysis of the amino acid sequence of the full-length PRO1069 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1069 amino acid sequence and the following Dayhoff sequences: CHIF_RAT, A55571, PLM_HUMAN, A40533, ATNG_BOVIN, RIC_MOUSE, PETD_SYNY3, VTBI_XENLA, A05009, and S75086.

Clone DNA59211-1450 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209960.

20 EXAMPLE 79: Isolation of cDNA Clones Encoding Human PRO1129

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as 98833. The Incyte EST cluster sequence no. 98833 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56038.

30 In light of an observed sequence homology between the DNA56038 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1335241, the Incyte EST clone 1335241 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 181 and is herein designated DNA59213-1487.

35 The full length clone shown in Figure 181 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 42-44 and ending at the stop codon found at nucleotide positions 1614-1616 (Figure 181; SEQ ID NO:263). The predicted polypeptide precursor is 524 amino acids long, has a calculated molecular weight of approximately 60,310 daltons and an estimated pI of approximately 7.46.

Analysis of the full-length PRO1129 sequence shown in Figure 182 (SEQ ID NO:264) evidences the presence of the following: type II transmembrane domains from about amino acid 13 to about amino acid 32 and from about amino acid 77 to about amino acid 102, a cytochrome P-450 cysteine heme-iron ligand signature sequence from about amino acid 461 to about amino acid 470 and potential N-glycosylation sites from about amino acid 112 to about amino acid 115 and from about amino acid 168 to about amino acid 171. Clone DNA59213-1487 has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209959.

Analysis of the amino acid sequence of the full-length PRO1129 polypeptide suggests that it possesses sequence similarity to the cytochrome P-450 family of proteins. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1129 amino acid sequence and the following Dayhoff sequences, AC004523_1, S45702, AF054821_1 and I53015.

EXAMPLE 80: Isolation of cDNA clones Encoding Human PRO1068

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, designated Incyte cluster no. 141736. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. One or more of the ESTs was derived from a human mast cell line from a patient with mast cell leukemia. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56094.

In light of an observed sequence homology between the DNA56094 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 004974, the Incyte EST clone 004974 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 183 and is herein designated as DNA59214-1449 (SEQ ID NO:265).

The full length clone shown in Figure 183 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 42-44 and ending at the stop codon found at nucleotide positions 414-416 (Figure 183; SEQ ID NO:265). The predicted polypeptide precursor (Figure 184, SEQ ID NO:266) is 124 amino acids long. PRO1068 has a calculated molecular weight of approximately 14,284 daltons and an estimated pI of approximately 8.14. The PRO1068 polypeptide has the following additional features, as indicated in Figure 184: a signal peptide sequence at about amino acids 1-20, a urotensin II signature sequence at about amino acids 118-123, a cell attachment sequence at about amino acids 64-66, and a potential cAMP- and cGMP-dependent protein kinase phosphorylation site at about amino acids 112-115.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 184 (SEQ ID NO:266), revealed homology between the PRO1068 amino acid sequence and the following Dayhoff sequences: HALBOP_1, MTV043_36,

ISO498, and P_R78445

Clone DNA59214-1449 was deposited with the ATCC on July 1, 1998 and is assigned ATCC deposit no.203046.

EXAMPLE 81: Isolation of cDNA clones Encoding Human PRO1066

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as 79066. The Incyte EST cluster sequence no. 79066 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or
10 BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56121.

15 In light of an observed sequence homology between the DNA56121 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1515315, the Incyte EST clone 1515315 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 185 and is herein designated DNA59215-1425.

20 The full length clone shown in Figure 185 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 176-178 and ending at the stop codon found at nucleotide positions 527-529 (Figure 185; SEQ ID NO:267). The predicted polypeptide precursor is 117 amino acids long, has a calculated molecular weight of approximately 12,911 daltons and an estimated pI of approximately 5.46. Analysis of the full-length PRO1066 sequence shown in Figure 186 (SEQ ID NO:268) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, a cAMP- and cGMP-
25 dependent protein kinase phosphorylation site from about amino acid 38 to about amino acid 41 and potential N-myristoylation sites from about amino acid 5 to about amino acid 10, from about amino acid 63 to about amino acid 68 and from about amino acid 83 to about amino acid 88. Clone UNQ524 (DNA59215-1425) has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209961.

30 Analysis of the amino acid sequence of the full-length PRO1066 polypeptide suggests that it does not possess significant sequence similarity to any known human protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1066 amino acid sequence and the following Dayhoff sequences, MOTI_HUMAN, AF025667_1, MTCY19H9_8 and RABIGKCH_1.

EXAMPLE 82: Isolation of cDNA Clones Encoding Human PRO1184

35 Use of the signal sequence algorithm described in Example 3 on ESTs from an Incyte database allowed identification a candidate sequence designated herein as DNA56375. This sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and

a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56375.

In light of an observed sequence homology between the DNA56375 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1428374, the Incyte EST clone 1428374 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 187.

The full length clone shown in Figure 187 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 106-108 and ending at the stop codon found at nucleotide positions 532-534 (Figure 187; SEQ ID NO:269). The predicted polypeptide precursor is 142 amino acids long, has a calculated molecular weight of approximately 15,690 daltons and an estimated pI of approximately 9.64. Analysis of the full-length PRO1184 sequence shown in Figure 188 (SEQ ID NO:270) evidences the presence of a signal peptide at about amino acids 1-38. Clone DNA59220-1514 has been deposited with the ATCC on June 9, 1998. It is understood that the deposited clone has the actual sequences and that representations are presented herein.

Analysis of the amino acid sequence of the full-length PRO1184 polypeptide suggests that it possesses some sequence identity with a protein called TIM from *Drosophila virilis*, designated "DVTIMS02_1" in the Dayhoff data base, (version 35.45 SwissProt 35). Other Dayhoff database (version 35.45 SwissProt 35) sequences having some degree of sequence identity with PRO1184 include: WIS1_SCHPO, F002186_1, ATAC00239124 and MSAIPRP_1.

EXAMPLE 83: Isolation of cDNA clones Encoding Human PRO1360

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST sequence from an Incyte database, designated DNA10572. This EST sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank, Merck/Wash. U.) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57314.

In light of an observed sequence homology between the DNA57314 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA406443, the Merck EST clone AA406443 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 189 and is herein designated as DNA59488-1603.

The full length clone shown in Figure 189 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 54-56 and ending at the stop codon found at nucleotide positions 909-911 (Figure 189; SEQ ID NO:271). The predicted polypeptide precursor (Figure 190, SEQ ID NO:272) is 285 amino acids long. PRO1360 has a calculated molecular weight of approximately 31,433 daltons and an estimated pI of approximately 7.32. Clone DNA59488-1603 was deposited with the ATCC on August 25, 1998 and is assigned ATCC deposit no. 203157.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 190 (SEQ ID NO:272), revealed sequence identity between the PRO1360 amino acid sequence and the following Dayhoff sequences: UN51_CAEEL, YD4B_SCHPO, AF000634_1, GFO_ZYMMO, YEIJ_SCHPO, D86566_1, ZMGFO_1, S76976, PPSA_SYNY3, and CEF28B1_4.

EXAMPLE 84: Isolation of cDNA clones Encoding Human PRO1029

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 18763. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57854.

In light of an observed sequence homology between the DNA57854 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T98880, the Merck EST clone T98880 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 191 and is herein designated as DNA59493-1420.

Clone DNA59493-1420 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 39-41 and ending at the stop codon at nucleotide positions 297-299 (Figure 191). The predicted polypeptide precursor is 86 amino acids long (Figure 192). The full-length PRO1029 protein shown in Figure 192 has an estimated molecular weight of about 9,548 daltons and a pI of about 8.52. Analysis of the full-length PRO1029 sequence shown in Figure 192 (SEQ ID NO:274) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19, an amino acid block having homology to bacterial rhodopsins retinal binding site protein from about amino acid 50 to about amino acid 61, a prenyl group binding site from about amino acid 83 to about amino acid 86 and a potential N-glycosylation site from about amino acid 45 to about amino acid 48. Clone DNA59493-1420 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203050.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 192 (SEQ ID NO:274), evidenced significant

homology between the PRO1029 amino acid sequence and the following Dayhoff sequences: S66088, AF031815_1, MM4A6L_1, PSEIS52a-1, S17699 and P_R63635.

EXAMPLE 85: Isolation of cDNA clones Encoding Human PRO1139

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 4461. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57312.

The DNA57312 consensus sequence included a 172 nucleotides long public EST (T62095, Merck/University of Washington public database). This EST clone, identified herein as a putative protein coding sequence, was purchased from Merck, and sequenced to provide the coding sequence of PRO1139 (Figure 193). As noted before, the deduced amino acid sequence of DNA59497-1496 shows a significant sequence identity with the deduced amino acid sequence of HSOBRGRP_1. The full-length protein (Figure 194) contains a putative signal peptide between amino acid residues 1 and about 28, and three putative transmembrane domains (approximate amino acid residues 33-52, 71-89, 98-120).

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EXAMPLE 86: Isolation of cDNA clones Encoding Human PRO1309

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to SLIT.

RNA for construction of cDNA libraries was isolated from human fetal brain tissue. The cDNA libraries used to isolate the cDNA clones encoding human PRO1309 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

30

The cDNA libraries (prepared as described above), were screened by hybridization with a synthetic oligonucleotide probe derived from the above described Incyte EST sequence:

5'-TCCGTGCAGGGGACGCCTTTCAGAACTGCGCCGAGTTAAGGAAC-3' (SEQ ID NO:279).

A cDNA clone was isolated and sequenced in entirety. The entire nucleotide sequence of DNA59588-1571 is shown in Figure 195 (SEQ ID NO:277). Clone DNA59588-1571 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 720-722 and a stop codon at nucleotide positions 2286-2288 (Figure 195; SEQ ID NO:277). The predicted polypeptide precursor is 522 amino acids

35

long. The signal peptide is approximately at 1-34 and the transmembrane domain is at approximately 428-450 of SEQ ID NO:278. Clone DNA59588-1571 has been deposited with ATCC and is assigned ATCC deposit no. 203106. The full-length PRO1309 protein shown in Figure 196 has an estimated molecular weight of about 58,614 daltons and a pI of about 7.42.

- 5 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 196 (SEQ ID NO:278), revealed sequence identity between the PRO1309 amino acid sequence and the following Dayhoff sequences: AB007876_1, GPV_MOUSE, ALS_RAT, P_R85889, LUM_CHICK, AB014462_1, PGS1_CANFA, CEM88_7, A58532 and GEN11209.

EXAMPLE 87: Isolation of cDNA Clones Encoding Human PRO1028

- 10 Use of the signal sequence algorithm described in Example 3 above allowed identification of a certain EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in
15 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA59603.

- 20 In light of an observed sequence homology between the DNA59603 sequence and an EST sequence contained within Incyte EST clone no. 1497725, the Incyte EST clone no. 1497725 was purchased and the cDNA insert was obtained and sequenced. It was found that the insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 197 and is herein designated as DNA59603-1419.

- The entire nucleotide sequence of DNA59603-1419 is shown in Figure 197 (SEQ ID NO:280). Clone DNA59603-1419 contains a single open reading frame with an apparent translational initiation site at nucleotide
25 positions 21-23 and ending at the stop codon at nucleotide positions 612-614 (Figure 197). The predicted polypeptide precursor is 197 amino acids long (Figure 198). The full-length PRO1028 protein shown in Figure 198 has an estimated molecular weight of about 20,832 daltons and a pI of about 8.74. Clone DNA59603-1419 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

- 30 Analyzing the amino acid sequence of SEQ ID NO:281, the putative signal peptide is at about amino acids 1-19 of SEQ ID NO:281. An N-glycosylation site is at about amino acids 35-38 of SEQ ID NO:281. A C-type lectin domain is at about amino acids 108-117 of SEQ ID NO:281, indicating that PRO513 may be related to or be a lectin. The corresponding nucleotides of these amino acid sequences or others can be routinely determined given the sequences provided herein.

EXAMPLE 88: Isolation of cDNA Clones Encoding Human PRO1027

Use of the signal sequence algorithm described in Example 3 above allowed identification of a certain EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The

5 homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56399.

10 In light of an observed sequence homology between the DNA56399 sequence and an EST sequence contained within Incyte EST clone no. 937605, the Incyte EST clone no. 937605 was purchased and the cDNA insert was obtained and sequenced. It was found that the insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 199 and is herein designated as DNA59605-1418.

The entire nucleotide sequence of DNA59605-1418 is shown in Figure 199 (SEQ ID NO:282). Clone

15 DNA59605-1418 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 31-33 and ending at the stop codon at nucleotide positions 262-264 (Figure 199). The predicted polypeptide precursor is 77 amino acids long (Figure 200). The full-length PRO1027 protein shown in Figure 200 has an estimated molecular weight of about 8,772 daltons and a pI of about 9.62. Clone DNA59605-1418 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains

20 the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analyzing the amino acid sequence of SEQ ID NO:283, the putative signal peptide is at about amino acids 1-33 of SEQ ID NO:283. The type II fibronectin collagen-binding domain begins at about amino acid 30 of SEQ ID NO:283. The corresponding nucleotides for these amino acid sequences and others can be routinely determined given the sequences provided herein. PRO1027 may be involved in tissue formation or repair.

25 The following Dayhoff designations appear to have some sequence identity with PRO1027: SFT2_YEAST; ATM3E9_2; A69826; YM16_MARPO; E64896; U60193_2; MTLRAJ205_1; MCU60315_70; SPAS_SHIFL; and S54213.

EXAMPLE 89: Isolation of cDNA Clones Encoding Human PRO1107

30 Use of the signal sequence algorithm described in Example 3 above allowed identification of a certain EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in

35 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence

obtained therefrom is herein designated DNA56402.

In light of an observed sequence homology between the DNA56402 sequence and an EST sequence contained within Incyte EST clone no. 3203694, the Incyte EST clone no. 3203694 was purchased and the cDNA insert was obtained and sequenced. It was found that the insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 201 and is herein designated as DNA59606-1471.

5 The entire nucleotide sequence of DNA59606-1471 is shown in Figure 201 (SEQ ID NO:284). Clone DNA59606-1471 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 244-246 and ending at the stop codon at nucleotide positions 1675-1677 of SEQ ID NO:284 (Figure 201). The predicted polypeptide precursor is 477 amino acids long (Figure 202). The full-length PRO1107 protein shown in Figure 202 has an estimated molecular weight of about 54,668 daltons and a pI of about 6.33.
10 Clone DNA59606-1471 has been deposited with ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO1107 polypeptide suggests that it possesses significant sequence similarity to phosphodiesterase I/nucleotide pyrophosphatase, human insulin receptor
15 tyrosine kinase inhibitor, alkaline phosphodiesterase and autotaxin, thereby indicating that PRO1107 may have at least one or all of the activities of these proteins, and that PRO1107 is a novel phosphodiesterase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO1107 amino acid sequence and at least the following Dayhoff sequences: AF005632_1, P_R79148, RNU78787_1, AF060218_4, A57080 and HUMATXT_1.

20

EXAMPLE 90: Isolation of cDNA clones Encoding Human PRO1140

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence, Incyte cluster sequence No. 135917. This sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary
25 EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained
30 therefrom is herein designated DNA56416.

In light of an observed sequence homology between DNA56416 and an EST sequence contained within Incyte EST clone no. 3345705, Incyte EST clone no. 3345705 was obtained and its insert sequenced. It was found that the insert encoded a full-length protein. The sequence, designated herein as DNA59607-1497, which is shown in Figure 203, is the full-length DNA sequence for PRO1140. Clone DNA59607-1497 was deposited
35 with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209946.

The entire nucleotide sequence of DNA59607-1497 is shown in Figure 203 (SEQ ID NO:286). Clone DNA59607-1497 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 210-212 and ending at the stop codon at nucleotide positions 975-977 (Figure 203). The predicted polypeptide precursor is 255 amino acids long (Figure 204). The full-length PRO1140 protein shown in Figure 204 has an estimated molecular weight of about 29,405 daltons and a pI of about 7.64. Analysis of the full-length PRO1140 sequence shown in Figure 204 (SEQ ID NO:287) evidences the presence of three transmembrane domains at about amino acids 101 to 118, 141 to 161 and 172 to 191.

5 Analysis of the amino acid sequence of the full-length PRO1140 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1140 amino acid sequence and the following Dayhoff sequences: AF023602_1, AF000368_1, CIN3_RAT, AF003373_1, GEN13279, and AF003372_1.

 Clone DNA59607-1497 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209946.

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EXAMPLE 91: Isolation of cDNA clones Encoding Human PRO1106

 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence. This sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte
15 Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated
20 DNA56423.

 In light of an observed sequence homology between DNA56423 and an EST sequence contained within Incyte EST clone no. 1711247, Incyte EST clone no. 1711247 was obtained and its insert sequenced. It was found that the insert encoded a full-length protein. The sequence, designated herein as DNA59609-1470, which is shown in Figure 205, is the full-length DNA sequence for PRO1106. Clone DNA59609-1470 was deposited
25 with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209963.

 The entire nucleotide sequence of DNA59609-1470 is shown in Figure 205 (SEQ ID NO:288). Clone DNA59609-1470 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 61-63 and ending at the stop codon at nucleotide positions 1468-1470 of SEQ ID NO:288 (Figure 205). The predicted polypeptide precursor is 469 amino acids long (Figure 206). The full-length PRO1106 protein
30 shown in Figure 206 has an estimated molecular weight of about 52,689 daltons and a pI of about 8.68. It is understood that the skilled artisan can construct the polypeptide or nucleic acid encoding therefor to exclude any one or more of all of these domains. For example, the transmembrane domain region(s) and/or either of the amino terminal or carboxyl end can be excluded. Clone DNA59609-1470 has been deposited with ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the
35 sequences provided herein are based on known sequencing techniques.

 Analysis of the amino acid sequence of the full-length PRO1106 polypeptide suggests that it possesses significant sequence similarity to the peroxisomal ca-dependent solute carrier, thereby indicating that PRO1106

may be a novel transporter. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO1106 amino acid sequence and at least the following Dayhoff sequences, AF004161_1, IG002N01_25, GDC_BOVIN and BT1_MAIZE.

EXAMPLE 92: Isolation of cDNA clones Encoding Human PRO1291

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 120480. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul
10 et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56425.

15 In light of an observed sequence homology between the DNA56425 sequence and an EST sequence encompassed within the Incyte EST clone no. 2798803, the Incyte EST clone 2798803 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 207 and is herein designated as DNA59610-1556.

20 Clone DNA59610-1556 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 61-63 and ending at the stop codon at nucleotide positions 907-909 (Figure 207). The predicted polypeptide precursor is 282 amino acids long (Figure 208). The full-length PRO1291 protein shown in Figure 208 has an estimated molecular weight of about 30,878 daltons and a pI of about 5.27. Analysis of the full-length PRO1291 sequence shown in Figure 208 (SEQ ID NO:291) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, a transmembrane domain from about amino acid 258 to about amino acid 281 and potential N-glycosylation sites from about amino acid 112 to about
25 amino acid 115, from about amino acid 160 to about amino acid 163, from about amino acid 190 to about amino acid 193, from about amino acid 196 to about amino acid 199, from about amino acid 205 to about amino acid 208, from about amino acid 216 to about amino acid 219 and from about amino acid 220 to about amino acid 223.. Clone DNA59610-1556 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209990.

30 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 208 (SEQ ID NO:291), evidenced significant homology between the PRO1291 amino acid sequence and the following Dayhoff sequences: HSU90552_1, HSU90144_1, AF033107_1, HSB73_1, HSU90142_1, GGCD80_1, P_W34452, MOG_MOUSE, B39371 and P_R71360.

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EXAMPLE 93: Isolation of cDNA clones Encoding Human PRO1105

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The
 5 homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56430.

10 In light of an observed sequence homology between the DNA56430 sequence and an EST sequence encompassed within the Incyte EST clone no. 1853047, the Incyte EST clone 1853047 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 209 and is herein designated as DNA59612-1466.

The entire nucleotide sequence of DNA59612-1466 is shown in Figure 209 (SEQ ID NO:292). Clone
 15 DNA59612-1466 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 28-30 and ending at the stop codon at nucleotide positions 568-570 of SEQ ID NO:292 (Figure 209). The predicted polypeptide precursor is 180 amino acids long (Figure 210). The full-length PRO1105 protein shown in Figure 210 has an estimated molecular weight of about 20,040 daltons and a pI of about 8.35. Clone DNA59612-1466 has been deposited with the ATCC on June 9, 1998. It is understood that the deposited clone
 20 has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analyzing Figure 210, a signal peptide is at about amino acids 1-19 of SEQ ID NO:293 and transmembrane domains are shown at about amino acids 80-99 and 145-162 of SEQ ID NO:293. It is understood that the skilled artisan could form a polypeptide with all of or any combination or individual selection
 25 of these regions. It is also understood that the corresponding nucleic acids can be routinely identified and prepared based on the information provided herein.

EXAMPLE 94: Isolation of cDNA clones Encoding Human PRO511

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST
 30 cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)
 35 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56434.

In light of an observed sequence homology between the DNA56434 sequence and an EST sequence encompassed within the Incyte EST clone no. 1227491, the Incyte EST clone 1227491 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 211 and is herein designated as DNA59613-1417.

The entire nucleotide sequence of DNA59613-1417 is shown in Figure 211 (SEQ ID NO:294). Clone DNA59613-1417 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 233-235 and ending at the stop codon at nucleotide positions 944-946 (Figure 211). The predicted polypeptide precursor is 237 amino acids long (Figure 212). The full-length PRO511 protein shown in Figure 212 has an estimated molecular weight of about 25,284 daltons and a pI of about 5.74. Clone DNA59613-1417 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analyzing the amino acid sequence of SEQ ID NO:295, the putative signal peptide is at about amino acids 1-25 of SEQ ID NO:295. The N-glycosylation sites are at about amino acids 45-48, 73-76, 107-110, 118-121, 132-135, 172-175, 175-178 and 185-188 of SEQ ID NO:295. An arthropod defensins conserved region is at about amino acids 176-182 of SEQ ID NO:295. A kringle domain begins at about amino acid 128 of SEQ ID NO:295 and a ly-6/u-PAR domain begins at about amino acid 6 of SEQ ID NO:295. The corresponding nucleotides of these amino acid sequences and others can be routinely determined given the sequences provided herein.

The designations appearing in a Dayhoff database with which PRO511 has some sequence identity are as follows: SSC20F10_1; SF041083; P_W26579; S44208; JC2394; PSTA_DICDI; A27020; S59310; RAG1_RABIT; and MUSBALBC1_1.

EXAMPLE 95: Isolation of cDNA clones Encoding Human PRO1104

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56446.

In light of an observed sequence homology between the DNA56446 sequence and an EST sequence encompassed within the Incyte EST clone no. 2837496, the Incyte EST clone 2837496 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 213 and is herein designated as DNA59616-1465.

The entire nucleotide sequence of DNA59616-1465 is shown in Figure 213 (SEQ ID NO:296). Clone DNA59616-1465 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 109-111 and ending at the stop codon at nucleotide positions 1132-1134 of SEQ ID NO:296 (Figure 213). The predicted polypeptide precursor is 341 amino acids long (Figure 214). The full-length PRO1104 protein shown in Figure 214 has an estimated molecular weight of about 36,769 daltons and a pI of about 9.03. Clone DNA59616-1465 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analyzing Figure 214, a signal peptide is at about amino acids 1-22 of SEQ ID NO:297. N-myristoylation sites are at about amino acids 41-46, 110-115, 133-138, 167-172 and 179-184 of SEQ ID NO:297.

10 EXAMPLE 96: Isolation of cDNA clones Encoding Human PRO1100

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In light of an observed sequence homology between the obtained consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2305379, the Incyte EST clone 2305379 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 215 and is herein designated as DNA59619-1464.

The entire nucleotide sequence of DNA59619-1464 is shown in Figure 215 (SEQ ID NO:298). Clone DNA59619-1464 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 33-35 and ending at the stop codon at nucleotide positions 993-995 of SEQ ID NO:298 (Figure 215). The predicted polypeptide precursor is 320 amino acids long (Figure 216). The full-length PRO1100 protein shown in Figure 216 has an estimated molecular weight of about 36,475 daltons and a pI of about 7.29. Clone DNA59619-1464 has been deposited with ATCC on July 1, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Upon analyzing SEQ ID NO:299, the approximate locations of the signal peptide, the transmembrane domains, an N-glycosylation site, an N-myristoylation site, a CUB domain and an amiloride-sensitive sodium channel domain are present. It is believed that PRO1100 may function as a channel. The corresponding nucleic acids for these amino acids and others can be routinely determined given SEQ ID NO:299..

EXAMPLE 97: Isolation of cDNA clones Encoding Human PRO836

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The
5 homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained is herein designated DNA56453.

10 In light of an observed sequence homology between the DNA56453 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2610075, the Incyte EST clone 2610075 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 217 and is herein designated as DNA59620-1463.

The entire nucleotide sequence of DNA59620-1463 is shown in Figure 217 (SEQ ID NO:300). Clone
15 DNA59620-1463 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 65-67 and ending at the stop codon at nucleotide positions 1448-1450 of SEQ ID NO:300 (Figure 217). The predicted polypeptide precursor is 461 amino acids long (Figure 218). The full-length PRO836 protein shown in Figure 218 has an estimated molecular weight of about 52,085 daltons and a pI of about 5.36. Analysis of the full-length PRO836 sequence shown in Figure 218 (SEQ ID NO:301) evidences the presence of the
20 following: a signal peptide, N-glycosylation sites, N-myristoylation sites, a domain conserved in the YJL126w/YLR351c/yhcX family of proteins, and a region having sequence identity with SLS1. Clone DNA59620-1463 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

25 Analysis of the amino acid sequence of the full-length PRO836 polypeptide suggests that it possesses some sequence similarity to SLS1, thereby indicating that PRO836 may be involved in protein translocation of the ER. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some homology between the PRO836 amino acid sequence and at least the following Dayhoff sequences, S58132, SPBC3B9_1, S66714, CRU40057_1 and IMA_CAEEL.

EXAMPLE 98: Isolation of cDNA clones Encoding Human PRO1141

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 11873. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank)
35 and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or

in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56518.

In light of an observed sequence homology between the DNA56518 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2679995, the Incyte EST clone 2679995 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 219 and is herein designated as DNA59625-1498.

Clone DNA59625-1498 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 204-206 and ending at the stop codon at nucleotide positions 945-947 (Figure 219). The predicted polypeptide precursor is 247 amino acids long (Figure 220). The full-length PRO1141 protein shown in Figure 220 has an estimated molecular weight of about 26,840 daltons and a pI of about 8.19. Analysis of the full-length PRO1141 sequence shown in Figure 220 (SEQ ID NO:303) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19 and transmembrane domains from about amino acid 38 to about amino acid 57, from about amino acid 67 to about amino acid 83, from about amino acid 117 to about amino acid 139 and from about amino acid 153 to about amino acid 170. Clone DNA59625-1498 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209992.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 220 (SEQ ID NO:303), evidenced significant homology between the PRO1141 amino acid sequence and the following Dayhoff sequences: CEVF36H2L_2, PCRB7PRJ_1, AB000506_1, LEU95008_1, MRU87980_15, YIGM_ECOLI, STU65700_1, GHU62778_1, CYST_SYNY3 and AF009567_1.

EXAMPLE 99: Isolation of cDNA clones Encoding Human PRO1132

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA35934. Based on the DNA35934 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1132.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-TCCTGTGACCACCCCTCTAACACC-3' (SEQ ID NO:310) and

reverse PCR primer: 5'-CTGGAACATCTGCTGCCCAGATTC-3' (SEQ ID NO:311).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus sequence which had the following nucleotide sequence:

5'-GTCGGATGACAGCAGCAGCCGCATCATCAATGGATCCGACTGCGATATGC-3' (SEQ ID NO:312).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1132 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1132 and the derived protein sequence for PRO1132.

The entire nucleotide sequence of PRO1132 is shown in Figure 225 (SEQ ID NO:308). Clone DNA59767-1489 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 354-356 and a stop codon at nucleotide positions 1233-1235 (Figure 225; SEQ ID NO:308). The predicted polypeptide precursor is 293 amino acids long. The signal peptide is at about amino acids 1-22 and the histidine active site is at about amino acids 104-109 of SEQ ID NO:309. Clone DNA59767-1489 has been deposited with ATCC (having the actual sequence rather than representations based on sequencing techniques as presented herein) and is assigned ATCC deposit no. 203108. The full-length PRO1132 protein shown in Figure 226 has an estimated molecular weight of about 32,020 daltons and a pI of about 8.7.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 226 (SEQ ID NO:309), revealed sequence identity between the PRO1132 amino acid sequence and the following Dayhoff sequences: SSU76256_1, P_W10694, MMAE000663_6, AF013988_1, U66061_8, MMAE000665_2, MMAE00066415, MMAE00066414, MMAE000665_4 and MMAE00066412.

EXAMPLE 100: Isolation of cDNA clones Encoding Human NL7 (PRO1346)

A single EST sequence (#1398422) was found in the LIFESEQ® database as described in Example 1 above. This EST sequence was renamed as DNA45668. Based on the DNA45668 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for NL7.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-CACACGTCCAACCTCAATGGGCAG-3' (SEQ ID NO:315)

reverse PCR primer: 5'-GACCAGCAGGGCCAAGGACAAGG-3' (SEQ ID NO:316)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45668 sequence which had the following nucleotide sequence:

hybridization probe:

5'-GTTCTCTGAGATGAAGATCCGGCCGGTCCGGGAGTACCGCTTAG-3'

(SEQ ID NO:317)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the NL7 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from a human fetal kidney library (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for NL7 (designated herein as DNA59776-1600 [Figure 227, SEQ ID NO:313]) and the derived protein sequence for NL7 (PRO1346).

The entire coding sequence of NL7 (PRO1346) is shown in Figure 227 (SEQ ID NO:313). Clone DNA59776-1600 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 1-3 and an apparent stop codon at nucleotide positions 1384-1386. The predicted polypeptide precursor is 461 amino acids long. The protein contains an apparent type II transmembrane domain at amino acid positions from about 31 to about 50; fibrinogen beta and gamma chains C-terminal domain signature starting at about amino acid position 409, and a leucine zipper pattern starting at about amino acid positions 140, 147, 154 and 161, respectively. Clone DNA59776-1600 has been deposited with ATCC and is assigned ATCC deposit no. 203128. The full-length NL7 protein shown in Figure 228 has an estimated molecular weight of about 50,744 daltons and a pI of about 6.38.

Based on a WU-BLAST2 sequence alignment analysis (using the WU-BLAST2 computer program) of the full-length sequence, NL7 shows significant amino acid sequence identity to a human microfibril-associated glycoprotein (1 MFA4_HUMAN); to known TIE-2 ligands and ligand homologues, ficolin, serum lectin and TGF-1 binding protein.

EXAMPLE 101: Isolation of cDNA clones Encoding Human PRO1131

A cDNA sequence isolated in the amylase screen described in Example 2 above is herein designated DNA43546 (see Figure 231; SEQ ID NO:320). The DNA43546 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA45627.

Based on the DNA45627 sequence, oligonucleotide probes were generated and used to screen a human library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

PCR primers (forward and 2 reverse) were synthesized:

forward PCR primer 5'-ATGCAGGCCAAGTACAGCAGCAC-3' (SEQ ID NO:321);

reverse PCR primer 1 5'-CATGCTGACGACTTCCTGCAAGC-3' (SEQ ID NO:322); and

reverse PCR primer 1 5'-CCACACAGTCTCTGCTTCTTGGG-3' (SEQ ID NO:323)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA45627 sequence which had the following nucleotide sequence:

hybridization probe

5'-ATGCTGGATGATGATGGGGACACCACCATGAGCCTGCATT-3' (SEQ ID NO:324).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1131 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 144-146, and a stop signal at nucleotide positions 984-986 (Figure 229; SEQ ID NO:318). The predicted polypeptide precursor is 280 amino acids long, has a calculated molecular weight of approximately 31,966 daltons and an estimated pI of approximately 6.26. The transmembrane domain sequence is at about 49-74 of SEQ ID NO:319 and the region having sequence identity with LDL receptors is about 50-265 of SEQ ID NO:319. PRO1131 contains potential N-linked glycosylation sites at amino acid positions 95-98 and 169-172 of SEQ ID NO:319. Clone DNA59777-1480 has been deposited with the ATCC and is assigned ATCC deposit no. 203111.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 230 (SEQ ID NO:319), evidenced some sequence identity between the PRO1131 amino acid sequence and the following Dayhoff sequences: AB010710_1, I49053, I49115, RNU56863_1, LY4A_MOUSE, I55686, MMU56404_1, I49361, AF030313_1 and MMU09739_1.

EXAMPLE 102: Isolation of cDNA clones Encoding Human PRO1281

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA35720. Based on the DNA35720 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1281.

PCR primers (forward and reverse) were synthesized:

forward PCR primers:

- 5'-TGGAAGGCTGCCGCAACGACAATC-3' (SEQ ID NO:327);
5'-CTGATGTGGCCGATGTTCTG-3' (SEQ ID NO:328); and
5'-ATGGCTCAGTGTGCAGACAG-3' (SEQ ID NO:329).

reverse PCR primers:

- 5'-GCATGCTGCTCCGTGAAGTAGTCC-3' (SEQ ID NO:330); and
5'-ATGCATGGGAAAGAAGGCCTGCCC-3' (SEQ ID NO:331).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA35720 sequence which had the following nucleotide sequence:

hybridization probe:

5'-TGCACTGGTGACCACGAGGGGGTGCATATAGCCATCTGGAGCTGAG-3' (SEQ ID NO:332).

- In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1281 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated human fetal liver.

- DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1281 (designated herein as DNA59820-1549 [Figure 232, SEQ ID NO:325]; and the derived protein sequence for PRO1281.

The entire coding sequence of PRO1281 is shown in Figure 232 (SEQ ID NO:325). Clone DNA59820-1549 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 228-230 and an apparent stop codon at nucleotide positions 2553-2555. The predicted polypeptide precursor is 775 amino acids long. The full-length PRO1281 protein shown in Figure 233 has an estimated molecular weight of about 85,481 daltons and a pI of about 6.92. Additional features include a signal peptide at about amino acids 1-15; and potential N-glycosylation sites at about amino acids 138-141 and 361-364.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 233 (SEQ ID NO:326), revealed some sequence identity between the PRO1281 amino acid sequence and the following Dayhoff sequences: S44860, CET24D1_1, CEC38H2_3, CAC2_HAECO, B3A2_HUMAN, S22373, CEF38A3_2, CEC34F6_2, CEC34F6_3, and CELT22B11_3.

Clone DNA59820-1549 has been deposited with ATCC and is assigned ATCC deposit no. 203129.

EXAMPLE 103: Isolation of cDNA clones Encoding Human PRO1064

A cDNA sequence isolated in the amylase screen described in Example 2 above was found, by the WU-BLAST2 sequence alignment computer program, to have no significant sequence identity to any known human protein. This cDNA sequence is herein designated DNA45288. The DNA45288 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA48609. Oligonucleotide primers based upon the DNA48609 sequence were then synthesized and employed to screen a human fetal kidney cDNA library which resulted in the identification of the DNA59827-1426 clone shown in Figure 234. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

The oligonucleotide probes employed were as follows:

forward PCR primer 5'-CTGAGACCCTGCAGCACCATCTG-3' (SEQ ID NO:336)

reverse PCR primer 5'-GGTGCTTCTTGAGCCCCACTTAGC-3' (SEQ ID NO:337)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA48609 sequence which had the following nucleotide sequence

hybridization probe

5'-AATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCGCTGT-3' (SEQ ID NO:338)

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 532-534 and a stop signal at nucleotide positions 991-993 (Figure 234, SEQ ID NO:333). The predicted polypeptide precursor is 153 amino acids long, has a calculated

molecular weight of approximately 17,317 daltons and an estimated pI of approximately 5.17. Analysis of the full-length PRO1064 sequence shown in Figure 235 (SEQ ID NO:334) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a transmembrane domain from about amino acid 89 to about amino acid 110, an indole-3-glycerol phosphate synthase homology block from about amino acid 74 to about amino acid 105 and a Myb DNA binding domain protein repeat protein homology block from about amino acid 114 to about amino acid 137. Clone DNA59827-1426 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203089.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 235 (SEQ ID NO:334), evidenced homology between the PRO1064 amino acid sequence and the following Dayhoff sequences: MMNP15PRO_1, BP187PLYH_1, CELF42G8_4, MMU58888_1, GEN14270, TUB8_SOLTU, RCN_MOUSE, HUMRBSY79_1, SESENODA_1 and A21467_1.

EXAMPLE 104: Isolation of cDNA clones Encoding Human PRO1379

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein DNA45232. Based on the DNA45232 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1379.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGGACACCGTACCCTGGTATCTGC-3' (SEQ ID NO:341)

reverse PCR primer 5'-CCAACTCTGAGGAGAGCAAGTGGC-3' (SEQ ID NO:342)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45232 sequence which had the following nucleotide sequence:

hybridization probe

5'-TGTATGTGCACACCCTCACCATCACCTCCAAGGGCAAGGAGAAC-3' (SEQ ID NO:343).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1379 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1379 which is designated herein as DNA59828-1608 and shown in Figure 237 (SEQ ID NO:339); and the derived protein sequence for PRO1379 (SEQ ID NO:340).

The entire coding sequence of PRO1379 is shown in Figure 237 (SEQ ID NO:339). Clone DNA59828-1608 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 10-12 and an apparent stop codon at nucleotide positions 1732-1734. The predicted polypeptide precursor is 574 amino acids long. The full-length PRO1379 protein shown in Figure 238 has an estimated molecular weight of about 65,355 daltons and a pI of about 8.73. Additional features include a signal peptide at about amino acids

1-17 and potential N-glycosylation sites at about amino acids 160-163, 287-290, and 323-326.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 238 (SEQ ID NO:340), revealed some homology between the PRO1379 amino acid sequence and the following Dayhoff sequences: YHY8_YEAST, AF040625_1, HP714394_1, and HIV18U45630_1.

5 Clone DNA59828-1608 has been deposited with ATCC and is assigned ATCC deposit no. 203158.

EXAMPLE 105: Isolation of cDNA Clones Encoding Human PRO844

10 An expressed sequence tag (EST) DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed sequence identity with aLP. Based on the information and discoveries provided herein, the clone for this EST, Incyte clone no. 2657496 from a cancerous lung library was further examined.

DNA sequencing of the insert for this clone gave a sequence (herein designated as DNA59838-1462; SEQ ID NO:344) which includes the full-length DNA sequence for PRO844 and the derived protein sequence for PRO844.

15 The entire nucleotide sequence of DNA59838-1462 is shown in Figure 239 (SEQ ID NO:344). Clone DNA59838-1462 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 5-7 and ending at the stop codon at nucleotide positions 338-340 of SEQ ID NO:344 (Figure 239). The predicted polypeptide precursor is 111 amino acids long (Figure 240). The full-length PRO844 protein shown in Figure 240 has an estimated molecular weight of about 12,050 daltons and a pI of about 5.45. Clone
20 UNQ544 DNA59838-1462 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO844 polypeptide suggests that it possesses significant sequence similarity to serine protease inhibitors, thereby indicating that PRO844 may be a novel
25 proteinase inhibitor. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO844 amino acid sequence and at least the following Dayhoff sequences, ALK1_HUMAN, P_P82403, P_P82402, ELAF_HUMAN and P_P60950.

EXAMPLE 106: Isolation of cDNA Clones Encoding Human PRO848

30 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in
35 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence

obtained therefrom is herein designated DNA55999.

In light of an observed sequence homology between the DNA55999 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2768571, the Incyte EST clone 2768571 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 241 and is herein designated as DNA59839-1461.

5 The entire nucleotide sequence of DNA59839-1461 is shown in Figure 241 (SEQ ID NO:346). Clone DNA59839-1461 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 146-148 and ending at the stop codon at nucleotide positions 1946-1948 of SEQ ID NO:346 (Figure 241). The predicted polypeptide precursor is 600 amino acids long (Figure 242). The full-length PRO848 protein shown in Figure 242 has an estimated molecular weight of about 68,536 daltons. Clone DNA59839-1461
10 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO848 polypeptide suggests that it may be a novel sialyltransferase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO848 amino acid sequence and at least the following Dayhoff
15 sequences, P_R78619 (GalNAc-alpha-2, 6-sialyltransferase), CAAG5_CHICK (alpha-n-acetylgalactosamide alpha-2, 6-sialyltransferase), HSU14550_1, CAG6_HUMAN and P_R63217 (human alpha-2, 3-sialyltransferase).

EXAMPLE 107: Isolation of cDNA Clones Encoding Human PRO1097

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single
20 EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)
25 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56006.

In light of an observed sequence homology between the DNA56006 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2408105, the Incyte EST clone 2408105 was purchased
30 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 243 and is herein designated as DNA59841-1460.

The entire nucleotide sequence of DNA59841-1460 is shown in Figure 243 (SEQ ID NO:348). Clone DNA59841-1460 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 3-5 and ending at the stop codon at nucleotide positions 276-278 of SEQ ID NO:348 (Figure 243).
35 The predicted polypeptide precursor is 91 amino acids long (Figure 244). The full-length PRO1097 protein shown in Figure 244 has an estimated molecular weight of about 10,542 daltons and a pI of about 10.04. Clone DNA59841-1460 has been deposited with ATCC on July 1, 1998. It is understood that the deposited clone has

the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analyzing Figure 244, the signal peptide is at about amino acids 1-20 of SEQ ID NO:349. The glycoprotease family protein domain starts at about amino acid 56, and the acyltransferase ChoActase/COT/CPT family peptide starts at about amino acid 49 of SEQ ID NO:349.

5

EXAMPLE 108: Isolation of cDNA clones Encoding Human PRO1153

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56008.

In light of an observed sequence homology between the DNA56008 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2472409, the Incyte EST clone 2472409 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 245 and is herein designated as DNA59842-1502.

The full length clone shown in Figure 245 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 92-94 and ending at the stop codon found at nucleotide positions 683-685 (Figure 245; SEQ ID NO:350). The predicted polypeptide precursor (Figure 246, SEQ ID NO:351) is 197 amino acids long. PRO1153 has a calculated molecular weight of approximately 21,540 daltons and an estimated pI of approximately 8.31. Clone DNA59842-1502 has been deposited with ATCC and is assigned ATCC deposit no. 209982. It is understood that the correct and actual sequence is in the deposited clone while herein are present representations based on current sequencing techniques which may have minor errors.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1153 shows some amino acid sequence identity to the following Dayhoff designations: S57447; SOYHRGPC_1; S46965; P_P82971; VCPHEROPH_1; EXTN_TOBAC; MLCB2548_9; ANXA_RABIT; JC5437 and SSGP_VOLCA.

EXAMPLE 109: Isolation of cDNA clones Encoding Human PRO1154

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in

Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56025.

5 In light of an observed sequence homology between the DNA56025 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2169375, the Incyte EST clone 2169375 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 247 and is herein designated as DNA59846-1503.

10 The full length clone shown in Figure 247 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 86-88 and ending at the stop codon found at nucleotide positions 2909-2911 (Figure 247; SEQ ID NO:352). The predicted polypeptide precursor (Figure 248, SEQ ID NO:353) is 941 amino acids long. PRO1154 has a calculated molecular weight of approximately 107,144 daltons and an estimated pI of approximately 6.26. Clone DNA59846-1503 has been deposited with ATCC and is assigned ATCC deposit no. 209978.

15 Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1154 shows sequence identity to at least the following Dayhoff designations: AB011097_1, AMPN_HUMAN, RNU76997_1, 159331, GEN14047, HSU62768_1, P_R51281, CET07F10_1, SSU66371_1, and AMPRE_HUMAN.

EXAMPLE 110: Isolation of cDNA clones Encoding Human PRO1181

20 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database, designated herein as 82468. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2
25 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56029.

30 In light of an observed sequence homology between the DNA56029 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2186536, the Incyte EST clone 2186536 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 249 and is herein designated as DNA59847-1511.

35 Clone DNA59847-1511 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 17-19 and ending at the stop codon at nucleotide positions 1328-1330 (Figure 249). The predicted polypeptide precursor is 437 amino acids long (Figure 250). The full-length PRO1181 protein shown in Figure 250 has an estimated molecular weight of about 46,363 daltons and a pI of about 6.22. Analysis of the full-length PRO1181 sequence shown in Figure 250 (SEQ ID NO:355) evidences the presence of the

following: a signal peptide from about amino acid 1 to about amino acid 15, potential N-glycosylation sites from about amino acid 46 to about amino acid 49, from about amino acid 189 to about amino acid 192 and from about amino acid 382 to about amino acid 385 and amino acid sequence blocks having homology to Ly-6/u-PAR domain proteins from about amino acid 287 to about amino acid 300 and from about amino acid 98 to about amino acid 111. Clone DNA59847-1511 has been deposited with ATCC on August 4, 1998 and is assigned
 5 ATCC deposit no. 203098.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 250 (SEQ ID NO:355), evidenced homology between the PRO1181 amino acid sequence and the following Dayhoff sequences: AF041083_1, P_W26579, RNMAGPIAN_1, CELT13C2_2, LMSAP2GN_1, S61882, CEF35C5_12, DP87_DICDI, GIU47631_1 and
 10 P_R07092.

EXAMPLE 111: Isolation of cDNA clones Encoding Human PRO1182

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database, designated herein as 146647. This EST cluster sequence was
 15 then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and
 20 assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56033.

In light of an observed sequence homology between the DNA56033 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2595195, the Incyte EST clone 2595195 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.
 25 The sequence of this cDNA insert is shown in Figure 251 and is herein designated as DNA59848-1512.

Clone DNA59848-1512 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 67-69 and ending at the stop codon at nucleotide positions 880-882 (Figure 251). The predicted polypeptide precursor is 271 amino acids long (Figure 252). The full-length PRO1182 protein shown in Figure 252 has an estimated molecular weight of about 28,665 daltons and a pI of about 5.33. Analysis of
 30 the full-length PRO1182 sequence shown in Figure 252 (SEQ ID NO:357) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, an amino acid block having homology to C-type lectin domain proteins from about amino acid 247 to about amino acid 256 and an amino acid sequence block having homology to C1q domain proteins from about amino acid 44 to about amino acid 77. Clone DNA59848-1512 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit
 35 no. 203088.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 252 (SEQ ID NO:357), evidenced significant

homology between the PRO1182 amino acid sequence and the following Dayhoff sequences: PSPD_BOVIN, CL43_BOVIN, CONG_BOVIN, P_W18780, P_R45005, P_R53257 and CELEGAP7_1.

EXAMPLE 112: Isolation of cDNA clones Encoding Human PRO1155

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single
5 EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of
expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary
EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The
homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in
Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)
10 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with
the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence
obtained therefrom is herein designated DNA56102.

In light of an observed sequence homology between the DNA56102 consensus sequence and an EST
sequence encompassed within the Incyte EST clone no. 2858870, the Incyte EST clone 2858870 was purchased
15 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.
The sequence of this cDNA insert is shown in Figure 253 and is herein designated as DNA59849-1504.

The full length clone shown in Figure 253 contained a single open reading frame with an apparent
translational initiation site at nucleotide positions 158-160 and ending at the stop codon found at nucleotide
positions 563-565 (Figure 253; SEQ ID NO:358). The predicted polypeptide precursor (Figure 254, SEQ ID
20 NO:359) is 135 amino acids long. PRO1155 has a calculated molecular weight of approximately 14,833 daltons
and an estimated pI of approximately 9.78. Clone DNA59849-1504 has been deposited with ATCC and is
assigned ATCC deposit no. 209986. It is understood that the actual clone has the correct sequence whereas
herein are only representations which are prone to minor sequencing errors.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-
25 length sequence, PRO1155 shows some amino acid sequence identity with the following Dayhoff designations:
TKNK_BOVIN; PVB19X587_1; AF019049_1; P_W00948; S72864; P_W00949; I62742; AF038501_1;
TKNG_HUMAN; and YAT1_RHOBL. Based on the information provided herein, PRO1155 may play a role
in providing neuroprotection and cognitive enhancement.

30 **EXAMPLE 113: Isolation of cDNA clones Encoding Human PRO1156**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single
EST cluster sequence from the Incyte database, designated herein as 138851. This EST cluster sequence was
then compared to a variety of expressed sequence tag (EST) databases which included public EST databases
(e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to
35 identify existing homologies. The homology search was performed using the computer program BLAST or
BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a
BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and

assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56261.

In light of an observed sequence homology between the DNA56261 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3675191, the Incyte EST clone 3675191 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

5 The sequence of this cDNA insert is shown in Figure 255 and is herein designated as DNA59853-1505.

The full length clone shown in Figure 255 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 212-214 and ending at the stop codon found at nucleotide positions 689-691 (Figure 255; SEQ ID NO:360). The predicted polypeptide precursor (Figure 256, SEQ ID NO:361) is 159 amino acids long. PRO1156 has a calculated molecular weight of approximately 17,476 daltons, 10 an estimated pI of approximately 9.15, a signal peptide sequence at about amino acids 1 to about 22, and potential N-glycosylation sites at about amino acids 27-30 and 41-44.

Clone DNA59853-1505 was deposited with the ATCC on June 16, 1998 and is assigned ATCC deposit no. 209985.

15 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence shown in Figure 256 (SEQ ID NO:361), revealed some homology between the PRO1156 amino acid sequence and the following Dayhoff sequences: D45027_1, P_R79914, JC5309, KBF2_HUMAN, AF010144_1, GEN14351, S68681, P_R79915, ZMTAC_3, and HUMCPGO_1.

20 EXAMPLE 114: Isolation of cDNA Clones Encoding Human PRO1098

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The 25 homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56377.

30 In light of an observed sequence homology between the DNA56377 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3050917, the Incyte EST clone 3050917 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 257 and is herein designated as DNA59854-1459.

35 The entire nucleotide sequence of DNA59854-1459 is shown in Figure 257 (SEQ ID NO:362). Clone DNA59854-1459 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon at nucleotide positions 292-294 of SEQ ID NO:362 (Figure 257). The predicted polypeptide precursor is 78 amino acids long (Figure 258). The full-length PRO1098 protein

shown in Figure 258 has an estimated molecular weight of about 8,396 daltons and a pI of about 7.66. Clone DNA59854-1459 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

- 5 Analyzing Figure 258, a signal peptide appears to be at about amino acids 1-19 of SEQ ID NO:363, an N-glycosylation site appears to be at about amino acids 37-40 of SEQ ID NO:363, and N-myristoylation sites appear to be at about 15-20, 19-24 and 60-65 of SEQ ID NO:363.

EXAMPLE 115: Isolation of cDNA clones Encoding Human PRO1127

- 10 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57959.

- 20 In light of an observed sequence homology between the DNA57959 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 685126, the Merck EST clone 685126 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 259 and is herein designated as DNA60283-1484.

- 25 The full length clone shown in Figure 259 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 126-128 and ending at the stop codon found at nucleotide positions 327-329 (Figure 259; SEQ ID NO:364). The predicted polypeptide precursor (Figure 260, SEQ ID NO:365) is 67 amino acids long including a signal peptide at about 1-29 of SEQ ID NO:365. PRO1127 has a calculated molecular weight of approximately 7,528 daltons and an estimated pI of approximately 4.95. Clone DNA60283-1484 was deposited with the ATCC on July 1, 1998 and is assigned ATCC deposit no. 203043. It is understood that the deposited clone has the actual sequence, whereas representations which may have minor sequencing errors are presented herein.

- 30 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 260 (SEQ ID NO:365), revealed some homology between the PRO1127 amino acid sequence and the following Dayhoff sequences: AF037218_48, P_W09638, HBA_HETPO, S39821, KR2_EBV, CET20D3_8, HCU37630_1, HS193B12_10, S40012 and TRITUBC_1.

35

EXAMPLE 116: Isolation of cDNA clones Encoding Human PRO1126

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56250.

In light of an observed sequence homology between the DNA56250 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1437250, the Incyte EST clone 1437250 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 261 and is herein designated as DNA60615-1483.

Clone DNA60615-1483 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 110-112 and ending at the stop codon at nucleotide positions 1316-1318 (Figure 261). The predicted polypeptide precursor is 402 amino acids long (Figure 262). The full-length PRO1126 protein shown in Figure 262 has an estimated molecular weight of about 45,921 daltons and a pI of about 8.60. Analysis of the full-length PRO1126 sequence shown in Figure 262 (SEQ ID NO:367) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25 and potential N-glycosylation sites from about amino acid 66 to about amino acid 69, from about amino acid 138 to about amino acid 141 and from about amino acid 183 to about amino acid 186. Clone DNA60615-1483 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209980.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 262 (SEQ ID NO:367), evidenced significant homology between the PRO1126 amino acid sequence and the following Dayhoff sequences: I73636, NOMR_HUMAN, MMUSMYOC3_1, HS454G6_1, P_R98225, RNU78105_1, RNU72487_1, AF035301_1, CEELC48E7_4 and CEF11C3_3.

EXAMPLE 117: Isolation of cDNA clones Encoding Human PRO1125

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence

obtained therefrom is herein designated DNA56540.

In light of an observed sequence homology between the DNA56540 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1486114, the Incyte EST clone 1486114 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 263 and is herein designated as DNA60615-1483.

5 The full length clone shown in Figure 263 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 47-49 and ending at the stop codon found at nucleotide positions 1388-1390 (Figure 263; SEQ ID NO:368). The predicted polypeptide precursor (Figure 264, SEQ ID NO:369) is 447 amino acids long. PRO1125 has a calculated molecular weight of approximately 49,798 daltons and an estimated pI of approximately 9.78. Clone DNA60619-1482 has been deposited with ATCC and is assigned
10 ATCC deposit no. 209993. It is understood that the clone has the actual sequence and that the sequences herein are representations based on current techniques which may be prone to minor errors.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1125 shows some sequence identity with the following Dayhoff designations: RCO1_NEUCR; S58306; PKWA_THECU; S76086; P_R85881; HET1_PODAN; SPU92792_1;
15 APAF_HUMAN; S76414 and S59317.

EXAMPLE 118: Isolation of cDNA clones Encoding Human PRO1186

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of
20 expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with
25 the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56748.

In light of an observed sequence homology between the DNA56748 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3476792, the Incyte EST clone 3476792 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.
30 The sequence of this cDNA insert is shown in Figure 265 and is herein designated as DNA60621-1516.

The full length clone shown in Figure 265 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 91-93 and ending at the stop codon found at nucleotide positions 406-408 (Figure 265; SEQ ID NO:370). The predicted polypeptide precursor (Figure 266, SEQ ID NO:371) is 105 amino acids long. The signal peptide is at amino acids 1-19 of SEQ ID NO:371. PRO1186 has a
35 calculated molecular weight of approximately 11,715 daltons and an estimated pI of approximately 9.05. Clone DNA60621-1516 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203091.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 266 (SEQ ID NO:371), revealed some sequence identity between the PRO1186 amino acid sequence and the following Dayhoff sequences: VPRA_DENPO, LFE4_CHICK, AF034208_1, AF030433_1, A55035, COL_RABIT, CELB0507_9, S67826_1, S34665 and CRU73817_1.

5

EXAMPLE 119: Isolation of cDNA clones Encoding Human PRO1198

An initial DNA sequence referred to herein as DNA52083 was identified using a yeast screen in a human umbilical vein endothelial cell cDNA library that preferentially represents the 5' ends of the primary cDNA clones. DNA52083 was compared to ESTs from public databases (e.g., GenBank), and a proprietary
10 EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. The ESTs were clustered and assembled into a consensus DNA sequence using the computer program "phrap" (Phil Green, University of Washington, Seattle, Washington). One or more of the ESTs was obtained from human breast skin tissue biopsy. This consensus sequence is designated herein as DNA52780.

15 In light of an observed sequence homology between the DNA52780 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3852910, the Incyte EST clone 3852910 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 267 and is herein designated as DNA60622-1525.

20 The full length DNA60622-1525 clone shown in Figure 267 (SEQ ID NO:372) contained a single open reading frame with an apparent translational initiation site at nucleotide positions 54 to 56 and ending at the stop codon found at nucleotide positions 741 to 743. The predicted polypeptide precursor, which is shown in Figure 268 (SEQ ID NO:373), is 229 amino acids long. PRO1198 has a calculated molecular weight of approximately 25,764 daltons and an estimated pI of approximately 9.17. There is a signal peptide sequence at about amino acids 1 through 34. There is sequence identity with glycosyl hydrolases family 31 protein at about amino acids
25 142 to about 175.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 268 (SEQ ID NO:373), revealed some homology between the PRO1198 amino acid sequence and the following Dayhoff sequences: ATF6H11_6, UCRI_RAT, TOBSUP2NT_1, RCUERF3_1, AMU88186_1, P_W22485, S56579, AF040711_1, DPP4_PIG.

30 Clone DNA60622-1525 was been deposited with the ATCC on August 4, 1998, and is assigned ATCC deposit no. 203090.

EXAMPLE 120: Isolation of cDNA clones Encoding Human PRO1158

35 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The

homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57248.

5 In light of an observed sequence homology between the DNA57248 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2640776, the Incyte EST clone 2640776 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 269 and is herein designated as DNA60625-1507.

10 The full length clone shown in Figure 269 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 163 to 165 and ending at the stop codon found at nucleotide positions 532 to 534 (Figure 269; SEQ ID NO:374). The predicted polypeptide precursor (Figure 270, SEQ ID NO:375) is 123 amino acids long. PRO1158 has a calculated molecular weight of approximately 13,113 daltons and an estimated pI of approximately 8.53. Additional features include a signal peptide sequence at about amino acids 1-19, a transmembrane domain at about amino acids 56-80, and a potential N-glycosylation site at
15 about amino acids 36-39. Clone DNA60625-1507 was deposited with the ATCC on June 16, 1998 and is assigned ATCC deposit no. 209975.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 270 (SEQ ID NO:375), revealed some homology between the PRO1158 amino acid sequence and the following Dayhoff sequences: ATAC00310510F18A8.10,
20 P_R85151, PHS2_SOLTU, RNMHCIBAC_1, RNA1FMHC_1, I68771, RNRT1A10G_1, PTPA_HUMAN, HUMGACA_1, and CHKPTPA_1.

EXAMPLE 121: Isolation of cDNA clones Encoding Human PRO1159

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single
25 EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)
30 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57221.

In light of an observed sequence homology between the DNA57221 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 376776, the Incyte EST clone 376776 was purchased
35 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 271 and is herein designated as DNA60627-1508.

Clone DNA60627-1508 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 92-94 and ending at the stop codon at nucleotide positions 362-364 (Figure 271). The predicted polypeptide precursor is 90 amino acids long (Figure 272). The full-length PRO1159 protein shown in Figure 272 has an estimated molecular weight of about 9,840 daltons and a pI of about 10.13. Analysis of the full-length PRO1159 sequence shown in Figure 272 (SEQ ID NO:377) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 15 and a potential N-glycosylation site from about amino acid 38 to about amino acid 41. Clone DNA60627-1508 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203092.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 272 (SEQ ID NO:377), evidenced significant homology between the PRO1159 amino acid sequence and the following Dayhoff sequences: AF016494_6, AF036708_20, DSSCUTE_1, D89100_1, S28060, MEFA_XENLA, AF020798_12, G70065, E64423, JQ2005.

EXAMPLE 122: Isolation of cDNA clones Encoding Human PRO1124

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56035.

In light of an observed sequence homology between the DNA56035 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2767646, the Incyte EST clone 2767646 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 273 and is herein designated as DNA60629-1481.

The full length clone shown in Figure 273 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 25-27 and ending at the stop codon found at nucleotide positions 2782-2784 (Figure 273; SEQ ID NO:378). The predicted polypeptide precursor (Figure 274, SEQ ID NO:379) is 919 amino acids long. PRO1124 has a calculated molecular weight of approximately 101,282 daltons and an estimated pI of approximately 5.37. Clone DNA60629-1481 has been deposited with the ATCC and is assigned ATCC deposit no. 209979. It is understood that the deposited clone has the actual sequence, whereas only representations based on current sequencing techniques which may include normal and minor errors, are provided herein.

Based on a WU-BLAST2 sequence alignment analysis of the full-length sequence, PRO1124 shows significant amino acid sequence identity to a chloride channel protein and to ECAM-1. Specifically, the following Dayhoff designations were identified as having sequence identity with PRO1124: ECLC_BOVIN,

AF001261_1, P_W06548, SSC6A10_1, AF004355_1, S76691, AF017642, BYU06866_2, CSA_DICDI and SAU47139_2.

EXAMPLE 123: Isolation of cDNA clones Encoding Human PRO1287

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to the fringe protein. This EST sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence obtained is herein designated DNA40568.

Based on the DNA40568 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1287. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, *supra*, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTCGGGGAAAGGGACTTGATGTTGG-3' (SEQ ID NO:382)

reverse PCR primer 1 5'-GCGAAGGTGAGCCTCTATCTCGTGCC-3' (SEQ ID NO:383)

reverse PCR primer 2 5'-CAGCCTACACGTATTGAGG-3' (SEQ ID NO:384)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40568 sequence which had the following nucleotide sequence

hybridization probe

5'-CAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTCCC-3' (SEQ ID NO:385).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1287 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human bone marrow tissue. The cDNA libraries used to isolated the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD;

pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1287 (designated herein as DNA61755-1554 [Figure 275, SEQ ID NO:380]) and the derived protein sequence for PRO1287.

5 The entire nucleotide sequence of DNA61755-1554 is shown in Figure 275 (SEQ ID NO:380). The full length clone contained a single open reading frame with an apparent translational initiation site at nucleotide positions 655-657 and a stop signal at nucleotide positions 2251-2253 (Figure 275, SEQ ID NO:380). The predicted polypeptide precursor is 532 amino acids long, has a calculated molecular weight of approximately 61,351 daltons and an estimated pI of approximately 8.77. Analysis of the full-length PRO1287 sequence shown
10 in Figure 276 (SEQ ID NO:381) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 27 and potential N-glycosylation sites from about amino acid 315 to about amino acid 318 and from about amino acid 324 to about amino acid 327. Clone DNA61755-1554 has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203112.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence
15 alignment analysis of the full-length sequence shown in Figure 276 (SEQ ID NO:381), evidenced significant homology between the PRO1287 amino acid sequence and the following Dayhoff sequences: CET24D1_1, EZRI_BOVIN, GGU19889_1, CC3_YEAST, S74244, NALS_MOUSE, MOES_PIG, S28660, S44860 and YNA4_CAEEL.

20 EXAMPLE 124: Isolation of cDNA clones Encoding Human PRO1312

DNA55773 was identified in a human fetal kidney cDNA library using a yeast screen that preferentially represents the 5' ends of the primary cDNA clones. Based on the DNA55773 sequence, oligonucleotides were synthesized for use as probes to isolate a clone of the full-length coding sequence for PRO1312.

The full length DNA61873-1574 clone shown in Figure 277 (SEQ ID NO:386) contained a single open
25 reading frame with an apparent translational initiation site at nucleotide positions 7-9 and ending at the stop codon found at nucleotide positions 643-645. The predicted polypeptide precursor is 212 amino acids long (Figure 278, SEQ ID NO:387). PRO1312 has a calculated molecular weight of approximately 24,024 daltons and an estimated pI of approximately 6.26. Other features include a signal peptide at about amino acids 1-14; a transmembrane domain at about amino acids 141-160, and potential N-glycosylation sites at about amino acids
30 76-79 and 93-96.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 278 (SEQ ID NO:387), revealed some homology between the PRO1312 amino acid sequence and the following Dayhoff sequences: GCINTALPH_1, GIBMUC1A_1, P_R96298, AF001406_1, PVU88874_1, P_R85151, AF041409_1, CELC50F2_7, C45875,
35 and AB009510_21.

Clone DNA61873-1574 has been deposited with ATCC and is assigned ATCC deposit no. 203132.

EXAMPLE 125: Isolation of cDNA clones Encoding Human PRO1192

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein DNA35924. Based on the DNA35924 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1192.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-CCGAGGCCATCTAGAGGCCAGAGC-3' (SEQ ID NO:390)

reverse PCR primer: 5'-ACAGGCAGAGCCAATGGCCAGAGC-3' (SEQ ID NO:391).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35924 sequence which had the following nucleotide sequence:

hybridization probe:

5'-GAGAGGACTGCGGGAGTTTGGGACCTTTGTGCAGACGTGCTCATG-3' (SEQ ID NO:392).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1192 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver and spleen tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1192 designated herein as DNA62814-1521 and shown in Figure 279 (SEQ ID NO:388); and the derived protein sequence for PRO1192 which is shown in Figure 280 (SEQ ID NO:389).

The entire coding sequence of PRO1192 is shown in Figure 279 (SEQ ID NO:388). Clone DNA62814-1521 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and an apparent stop codon at nucleotide positions 766-768. The predicted polypeptide precursor is 215 amino acids long. The predicted polypeptide precursor has the following features: a signal peptide at about amino acids 1-21; a transmembrane domain at about amino acids 153-176; potential N-glycosylation sites at about amino acids 39-42 and 118-121; and homology with myelin P0 proteins at about amino acids 27-68 and 99-128 of Figure 280. The full-length PRO1192 protein shown in Figure 280 has an estimated molecular weight of about 24,484 daltons and a pI of about 6.98.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 280 (SEQ ID NO:389), revealed homology between the PRO1192 amino acid sequence and the following Dayhoff sequences: GEN12838, MYP0_HUMAN, AF049498_1, GEN14531, P_W14146, HS46KDA_1, CINB_RAT, OX2G_RAT, D87018_1, and D86996_2.

Clone DNA62814-1521 was deposited with the ATCC on August 4, 1998, and is assigned ATCC deposit no. 203093.

EXAMPLE 126: Isolation of cDNA clones Encoding Human PRO1160

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA40650. Based on the DNA40650 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1160.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCTCCCTGATCTTCATGTCACCACC-3' (SEQ ID NO:395)

reverse PCR primer 5'-CAGGGACACACTCTACCATTCTGGGAG-3' (SEQ ID NO:396)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40650 sequence which had the following nucleotide sequence

hybridization probe

5'-CCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTC-3' (SEQ ID NO:397)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1160 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human breast tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1160 (designated herein as DNA62872-1509 [Figure 281, SEQ ID NO: 393]) and the derived protein sequence for PRO1160.

The entire nucleotide sequence of DNA62872-1509 is shown in Figure 281 (SEQ ID NO:393). Clone DNA62872-1509 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 40-42 and ending at the stop codon at nucleotide positions 310-312 (Figure 281). The predicted polypeptide precursor is 90 amino acids long (Figure 282). The full-length PRO1160 protein shown in Figure 282 has an estimated molecular weight of about 9,039 daltons and a pI of about 4.37. Analysis of the full-length PRO1160 sequence shown in Figure 282 (SEQ ID NO:394) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19 and a protein kinase C phosphorylation site from about amino acid 68 to about amino acid 70. Clone DNA62872-1509 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203100.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 282 (SEQ ID NO:394), evidenced significant homology between the PRO1160 amino acid sequence and the following Dayhoff sequences: B30305, GEN13490, I53641, S53363, HA34_BRELC, SP96_DICDI, S36326, SSU51197_10, MUC1_XENLA, TCU32448_1 and AF000409_1.

EXAMPLE 127: Isolation of cDNA clones Encoding Human PRO1187

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of

expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57726.

In light of an observed sequence homology between the DNA57726 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 358563, the Incyte EST clone 358563 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 283 and is herein designated as DNA62876-1517.

The full length clone shown in Figure 283 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and ending at the stop codon found at nucleotide positions 481-483 (Figure 283; SEQ ID NO:398). The predicted polypeptide precursor (Figure 284, SEQ ID NO:399) is 120 amino acids long. The signal peptide is at about amino acids 1-17 of SEQ ID NO:399. PRO1187 has a calculated molecular weight of approximately 12,925 daltons and an estimated pI of approximately 9.46. Clone DNA62876-1517 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203095. It is understood that the deposited clone contains the actual sequence and that the representations herein may have minor sequencing errors.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 284 (SEQ ID NO:399), revealed some sequence identity (and therefore some relation) between the PRO1187 amino acid sequence and the following Dayhoff sequences: MGNENDOBX_1, CELF41G3_9, AMPG_STRLI, HSBBOVHERL_2, LEEXTEN10_1, AF029958_1 and P_W04957.

25 EXAMPLE 128: Isolation of cDNA clones Encoding Human PRO1185

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56426.

In light of an observed sequence homology between the DNA56426 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3284411, the Incyte EST clone 3284411 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 285 and is herein designated as DNA62881-1515.

The full length DNA62881-1515 clone shown in Figure 285 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 4-6 and ending at the stop codon found at nucleotide positions 598-600 (Figure 285; SEQ ID NO:400). The predicted polypeptide precursor (Figure 286, SEQ ID NO:401) is 198 amino acids long. The signal peptide is at about amino acids 1-21 of SEQ ID NO:401.

5 PRO1185 has a calculated molecular weight of approximately 22,105 daltons and an estimated pI of approximately 7.73. Clone DNA62881-1515 has been deposited with the ATCC and is assigned ATCC deposit no. 203096.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 286 (SEQ ID NO:401), revealed some sequence
10 identity between the PRO1185 amino acid sequence and the following Dayhoff sequences: TUP1_YEAST, AF041382_1, MAOM_SOLTU, SPPBPHU9_1, I41024, EPCPLCFail_1, HSPLEC_1, YKL4_CAEEL, A44643, TGU65922_1.

EXAMPLE 129: Isolation of cDNA clones Encoding Human PRO1345

15 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA47364. Based on the DNA47364 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1345.

20 PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCTGGTTATCCCCAGGAAGTCCGAC-3' (SEQ ID NO:404)

reverse PCR primer 5'-CTCTTGCTGCTGCGACAGGCCTC-3' (SEQ ID NO:405)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47364 sequence which had the following nucleotide sequence

25 hybridization probe

5'-CGCCCTCCAAGACTATGGTAAAAGGAGCCTGCCAGGTGTCAATGAC-3' (SEQ ID NO:406)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1345 gene using the probe oligonucleotide and one of the PCR primers. RNA
30 for construction of the cDNA libraries was isolated from human breast carcinoma tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1345 (designated herein as DNA64852-1589 [Figure 287, SEQ ID NO:402]) and the derived protein sequence for PRO1345.

The entire nucleotide sequence of DNA64852-1589 is shown in Figure 287 (SEQ ID NO:402). Clone
35 DNA64852-1589 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 7-9 or 34-36 and ending at the stop codon at nucleotide positions 625-627 (Figure 287). The predicted polypeptide precursor is 206 amino acids long (Figure 288). The full-length PRO1345 protein shown in Figure

288 has an estimated molecular weight of about 23,190 daltons and a pI of about 9.40. Analysis of the full-length PRO1345 sequence shown in Figure 288 (SEQ ID NO:403) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31 or from about amino acid 10 to about amino acid 31 and a C-type lectin domain signature sequence from about amino acid 176 to about amino acid 190. Clone DNA64852-1589 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203127.

5 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 288 (SEQ ID NO:403), evidenced significant homology between the PRO1345 amino acid sequence and the following Dayhoff sequences: BTU22298_1, TETN_CARSP, TETN_HUMAN, MABA_RAT, S34198, P_W13144, MACMBPA_1, A46274, PSPD_RAT AND P_R32188.

10 EXAMPLE 130: Isolation of cDNA clones Encoding Human PRO1245

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary
15 EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence
20 obtained therefrom is herein designated DNA56019.

In light of an observed sequence homology between the DNA56019 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1327836, the Incyte EST clone 1327836 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 289 and is herein designated as DNA64884-1527.

25 The full length clone shown in Figure 289 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 79-81 and ending at the stop codon found at nucleotide positions 391-393 (Figure 289; SEQ ID NO:407). The predicted polypeptide precursor (Figure 290, SEQ ID NO:408) is 104 amino acids long, with a signal peptide sequence at about amino acid 1 to about amino acid 18. PRO1245 has a calculated molecular weight of approximately 10,100 daltons and an estimated pI of
30 approximately 8.76.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 290 (SEQ ID NO:408), revealed some homology between the PRO1245 amino acid sequence and the following Dayhoff sequences: SYA_THETH, GEN11167, MTV044_4, AB011151_1, RLAJ2750_3, SNEIPTRA_1, S63624, C28391, A37907, and S14064.

35 Clone DNA64884-1245 was deposited with the ATCC on August 25, 1998 and is assigned ATCC deposit no. 203155.

EXAMPLE 131: Isolation of cDNA clones Encoding Human PRO1358

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 88718, the Incyte EST clone 88718 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 291 and is herein designated as DNA64890-1612.

The full length clone shown in Figure 291 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 86 through 88 and ending at the stop codon found at nucleotide positions 1418 through 1420 (Figure 291; SEQ ID NO:409). The predicted polypeptide precursor (Figure 292, SEQ ID NO:410) is 444 amino acids long. The signal peptide is at about amino acids 1-18 of SEQ ID NO:410. PRO1358 has a calculated molecular weight of approximately 50,719 daltons and an estimated pI of approximately 8.82. Clone DNA64890-1612 was deposited with the ATCC on August 18, 1998 and is assigned ATCC deposit no. 203131.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 292 (SEQ ID NO:410), revealed sequence identity between the PRO1358 amino acid sequence and the following Dayhoff sequences: P_W07607, AB000545_1, AB000546_1, A1AT_RAT, AB015164_1, P_P50021, COTR_CAVPO, and HAMHPP_1. The variants claimed in this application exclude these sequences.

EXAMPLE 132: Isolation of cDNA clones Encoding Human PRO1195

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55716.

In light of an observed sequence homology between the DNA55716 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3252980, the Incyte EST clone 3252980 was purchased

and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 293 and is herein designated as DNA65412-1523.

The full length clone shown in Figure 293 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon found at nucleotide positions 511-513 (Figure 293; SEQ ID NO:411). The predicted polypeptide precursor (Figure 294, SEQ ID NO:412) is 151 amino acids long. The signal sequence is at about amino acids 1-22 of SEQ ID NO:412. PRO1195 has a calculated molecular weight of approximately 17,277 daltons and an estimated pI of approximately 5.33. Clone DNA65412-1523 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203094.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 294 (SEQ ID NO:412), revealed some sequence identity between the PRO1195 amino acid sequence and the following Dayhoff sequences: MMU28486_1, AF044205_1, P_W31186, CELK03C7_1, F69034, EF1A_METVA, AF024540_1, SSU90353_1, MRSP_STAAU and P_R97680.

EXAMPLE 133: Isolation of cDNA clones Encoding Human PRO1270

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57951.

In light of an observed sequence homology between the DNA57951 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 124878, the Merck EST clone 124878 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 295 and is herein designated as DNA66308-1537.

Clone DNA66308-1537 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 103-105 and ending at the stop codon at nucleotide positions 1042-1044 (Figure 295). The predicted polypeptide precursor is 313 amino acids long (Figure 296). The full-length PRO1270 protein shown in Figure 296 has an estimated molecular weight of about 34,978 daltons and a pI of about 5.71. Analysis of the full-length PRO1270 sequence shown in Figure 296 (SEQ ID NO:414) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 16, a potential N-glycosylation site from about amino acid 163 to about amino acid 166 and glycosaminoglycan attachment sites from about amino acid 74 to about amino acid 77 and from about amino acid 289 to about amino acid 292. Clone DNA66308-1537 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203159.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 296 (SEQ ID NO:414), evidenced significant homology between the PRO1270 amino acid sequence and the following Dayhoff sequences: XLU86699_1, S49589, FIBA_PARPA, FIBB_HUMAN, P_R47189, AF004326_1, DRTENASCN_1, AF004327_1, P_W01411 and FIBG_BOVIN.

5

EXAMPLE 134: Isolation of cDNA clones Encoding Human PRO1271

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary
 10 EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence
 15 obtained therefrom is herein designated DNA57955.

In light of an observed sequence homology between the DNA57955 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA625350, the Merck EST clone AA625350 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 297 and is herein designated as DNA66309-1538.

20 Clone DNA66309-1538 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 94-96 and ending at the stop codon at nucleotide positions 718-720 (Figure 297). The predicted polypeptide precursor is 208 amino acids long (Figure 298). The full-length PRO1271 protein shown in Figure 298 has an estimated molecular weight of about 21,531 daltons and a pI of about 8.99. Analysis of the full-length PRO1271 sequence shown in Figure 298 (SEQ ID NO:416) evidences the presence of the
 25 following: a signal peptide from about amino acid 1 to about amino acid 31 and a transmembrane domain from about amino acid 166 to about amino acid 187. Clone DNA66309-1538 has been deposited with ATCC on September 15, 1998 and is assigned ATCC deposit no. 203235.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 298 (SEQ ID NO:416), evidenced significant
 30 homology between the PRO1271 amino acid sequence and the following Dayhoff sequences: S57180, S63257, AGA1_YEAST, BPU43599_1, YS8A_CAEEL, S67570, LSU54556_2, S70305, VGLX_HSVB, and D88733_1.

EXAMPLE 135: Isolation of cDNA clones Encoding Human PRO1375

35 A Merck/Wash. U. database was searched and a Merck EST was identified. This sequence was then put in a program which aligns it with other sequences from the Swiss-Prot public database, public EST databases (e.g., GenBank, Merck/Wash. U.), and a proprietary EST database (LIFESEQ®, Incyte

Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the extracellular domain (ECD) protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

A consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is designated herein "DNA67003".

Based on the DNA67003 consensus sequence, the nucleic acid (SEQ ID NO:417) was identified in a human pancreas library. DNA sequencing of the clone gave the full-length DNA sequence for PRO1375 and the derived protein sequence for PRO1375.

The entire coding sequence of PRO1375 is shown in Figure 299 (SEQ ID NO:417). Clone DNA67004-1614 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 104-106 and an apparent stop codon at nucleotide positions 698-700 of SEQ ID NO:417. The predicted polypeptide precursor is 198 amino acids long. The transmembrane domains are at about amino acids 11-28 (type II) and 103-125 of SEQ ID NO:418. Clone DNA67004-1614 has been deposited with ATCC and is assigned ATCC deposit no. 203115. The full-length PRO1375 protein shown in Figure 300 has an estimated molecular weight of about 22,531 daltons and a pI of about 8.47.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 300 (SEQ ID NO:418), revealed sequence identity between the PRO1375 amino acid sequence and the following Dayhoff sequences: AF026198_5, CELR12C12_5, S73465, Y011_MYCPN, S64538_1, P_P8150, MUVSHPO10_1, VSH_MUMPL and CVU59751_5.

EXAMPLE 136: Isolation of cDNA clones Encoding Human PRO1385

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57952.

In light of an observed sequence homology between the DNA57952 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3129630, the Incyte EST clone 3129630 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 301 and is herein designated as DNA68869-1610.

Clone DNA68869-1610 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 26-28 and ending at the stop codon at nucleotide positions 410-412 (Figure 301). The predicted polypeptide precursor is 128 amino acids long (Figure 302). The full-length PRO1385 protein shown in Figure 302 has an estimated molecular weight of about 13,663 daltons and a pI of about 10.97. Analysis of the full-length PRO1385 sequence shown in Figure 302 (SEQ ID NO:420) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, and glycosylaminoglycan attachment sites from about amino acid 82 to about amino acid 85 and from about amino acid 91 to about amino acid 94. Clone DNA68869-1610 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203164.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 302 (SEQ ID NO:420), evidenced low homology between the PRO1385 amino acid sequence and the following Dayhoff sequences: CELT14A8_1, LMNACHRA1_1, HXD9_HUMAN, CHKCMLF_1, HS5PP34_2, DMDRING_1, A37107_1, MMLUNGENE_1, PUM_DROME and DMU25117_1.

15 EXAMPLE 137: Isolation of cDNA clones Encoding Human PRO1387

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56259.

In light of an observed sequence homology between the DNA56259 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3507924, the Incyte EST clone 3507924 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 303 and is herein designated as DNA68872-1620.

Clone DNA68872-1620 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 85-87 and ending at the stop codon at nucleotide positions 1267-1269 (Figure 303). The predicted polypeptide precursor is 394 amino acids long (Figure 304). The full-length PRO1387 protein shown in Figure 304 has an estimated molecular weight of about 44,339 daltons and a pI of about 7.10. Analysis of the full-length PRO1387 sequence shown in Figure 304 (SEQ ID NO:422) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19, a transmembrane domain from about amino acid 275 to about amino acid 296, potential N-glycosylation sites from about amino acid 76 to about amino acid 79, from about amino acid 231 to about amino acid 234, from about amino acid 302 to about amino acid 305, from about amino acid 307 to about amino acid 310 and from about amino acid 376 to about amino acid

379, and amino acid sequence blocks having homology to myelin p0 protein from about amino acid 210 to about amino acid 239 and from about amino acid 92 to about amino acid 121. Clone DNA68872-1620 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203160.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 304 (SEQ ID NO:422), evidenced significant
 5 homology between the PRO1387 amino acid sequence and the following Dayhoff sequences: P_W36955, MYPO_HETFR, HS46KDA_1, AF049498_1, MYO0_HUMAN, AF030454_1, A53268, SHPTCRA_1, P_W14146 and GEN12838.

EXAMPLE 138: Isolation of cDNA clones Encoding Human PRO1384

10 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA54192. Based on the DNA54192 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1384.

PCR primers (forward and reverse) were synthesized:

15 forward PCR primer 5'-TGCAGCCCCTGTGACACAACTGG-3' (SEQ ID NO:425)

reverse PCR primer 5'-CTGAGATAACCGAGCCATCCTCCAC-3' (SEQ ID NO:426)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA54192 sequence which had the following nucleotide sequence:

hybridization probe

20 5'-GGAGATAGCTGCTATGGGTTCTTCAGGCACAACTTAACATGGGAAG-3' (SEQ ID NO:427)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1384 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver.

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1384 (designated herein as DNA71159-1617 [Figure 305, SEQ ID NO:423]; and the derived protein sequence for PRO1384.

The entire coding sequence of PRO1384 is shown in Figure 305 (SEQ ID NO:423). Clone DNA71159-1617 contains a single open reading frame with an apparent translational initiation site at nucleotide positions
 30 182-184 and an apparent stop codon at nucleotide positions 869-871. The predicted polypeptide precursor is 229 amino acids long. The full-length PRO1384 protein shown in Figure 306 has an estimated molecular weight of about 26,650 daltons and a pI of about 8.76. Additional features include a type II transmembrane domain at about amino acids 32-57, and potential N-glycosylation sites at about amino acids 68-71, 120-123, and 134-137.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence
 35 alignment analysis of the full-length sequence shown in Figure 306 (SEQ ID NO:424), revealed homology between the PRO1384 amino acid sequence and the following Dayhoff sequences: AF054819_1, HSAJ1687_1, AF009511_1, AB010710_1, GEN13595, HSAJ673_1, GEN13961, AB005900_1, LECH_CHICK, AF021349_1,

and NK13_RAT.

Clone DNA71159-1617 has been deposited with ATCC and is assigned ATCC deposit no. 203135.

EXAMPLE 139: Use of PRO as a hybridization probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

5 DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

10 Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

15

EXAMPLE 140: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

20 The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., *Gene*, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode
25 for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

30 The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

35 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the

protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin

from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4 % mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

- 5 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 141: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

- 10 The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-PRO.

- 15 In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μ g pRK5-PRO DNA is mixed with about 1 μ g DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in 500 μ l of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl_2 . To this mixture is added, dropwise, 500 μ l of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO_4 , and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

- 20 Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μ Ci/ml ^{35}S -cysteine and 200 μ Ci/ml ^{35}S -methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

- 25 In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompanyrac et al., *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μ g/ml bovine insulin and 35 0.1 μ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO_4 or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S -methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni^{2+} -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect[®] (Quiagen), Dosper[®] or Fugene[®] (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^5 cells/mL. The cell media is exchanged with fresh media by

centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

25 EXAMPLE 142: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

5 **EXAMPLE 143: Expression of PRO in Baculovirus-Infected Insect Cells**

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

15 Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

20 Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

35 Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 144: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 145: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody

is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 146: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the

solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

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EXAMPLE 147: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

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In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

25

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

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By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

35

Deposit of Material

The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC):

Table 2

<u>5</u>	<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
	DNA16422-1209	209929	June 2, 1998
	DNA16435-1208	209930	June 2, 1998
	DNA21624-1391	209917	June 2, 1998
	DNA23334-1392	209918	June 2, 1998
10	DNA26288-1239	209792	April 21, 1998
	DNA26843-1389	203099	August 4, 1998
	DNA26844-1394	209926	June 2, 1998
	DNA30862-1396	209920	June 2, 1998
	DNA35680-1212	209790	April 21, 1998
15	DNA40621-1440	209922	June 2, 1998
	DNA44161-1434	209907	May 27, 1998
	DNA44694-1500	203114	August 11, 1998
	DNA45495-1550	203156	August 25, 1998
	DNA47361-1154	209431	November 7, 1997
20	DNA47394-1572	203109	August 11, 1998
	DNA48320-1433	209904	May 27, 1998
	DNA48334-1435	209924	June 2, 1998
	DNA48606-1479	203040	July 1, 1998
	DNA49141-1431	203003	June 23, 1998
25	DNA49142-1430	203002	June 23, 1998
	DNA49143-1429	203013	June 23, 1998
	DNA49647-1398	209919	June 2, 1998
	DNA49819-1439	209931	June 2, 1998
	DNA49820-1427	209932	June 2, 1998
30	DNA49821-1562	209981	June 16, 1998
	DNA52192-1369	203042	July 1, 1998
	DNA52598-1518	203107	August 11, 1998
	DNA53913-1490	203162	August 25, 1998
	DNA53978-1443	209983	June 16, 1998
35	DNA53996-1442	209921	June 2, 1998
	DNA56041-1416	203012	June 23, 1998
	DNA56047-1456	209948	June 9, 1998
	DNA56050-1455	203011	June 23, 1998
	DNA56110-1437	203113	August 11, 1998
40	DNA56113-1378	203049	July 1, 1998
	DNA56410-1414	209923	June 2, 1998
	DNA56436-1448	209902	May 27, 1998
	DNA56855-1447	203004	June 23, 1998
	DNA56859-1445	203019	June 23, 1998
45	DNA56860-1510	209952	June 9, 1998
	DNA56865-1491	203022	June 23, 1998
	DNA56866-1342	203023	June 23, 1998
	DNA56868-1209	203024	June 23, 1998
	DNA56869-1545	203161	August 25, 1998
50	DNA56870-1492	209925	June 2, 1998
	DNA57033-1403	209905	May 27, 1998
	DNA57037-1444	209903	May 27, 1998
	DNA57129-1413	209977	June 16, 1998

	DNA57690-1374	209950	June 9, 1998
	DNA57693-1424	203008	June 23, 1998
	DNA57694-1341	203017	June 23, 1998
	DNA57695-1340	203006	June 23, 1998
	DNA57699-1412	203020	June 23, 1998
5	DNA57702-1476	209951	June 9, 1998
	DNA57704-1452	209953	June 9, 1998
	DNA57708-1411	203021	June 23, 1998
	DNA57710-1451	203048	July 1, 1998
	DNA57711-1501	203047	July 1, 1998
10	DNA57827-1493	203045	July 1, 1998
	DNA57834-1339	209954	June 9, 1998
	DNA57836-1338	203025	June 23, 1998
	DNA57838-1337	203014	June 23, 1998
	DNA57844-1410	203010	June 23, 1998
15	DNA58721-1475	203110	August 11, 1998
	DNA58723-1588	203133	August 18, 1998
	DNA58737-1473	203136	August 18, 1998
	DNA58743-1609	203154	August 25, 1998
	DNA58846-1409	209957	June 9, 1998
20	DNA58848-1472	209955	June 9, 1998
	DNA58849-1494	209958	June 9, 1998
	DNA58850-1495	209956	June 9, 1998
	DNA58853-1423	203016	June 23, 1998
	DNA58855-1422	203018	June 23, 1998
25	DNA59205-1421	203009	June 23, 1998
	DNA59211-1450	209960	June 9, 1998
	DNA59213-1487	209959	June 9, 1998
	DNA59214-1449	203046	July 1, 1998
	DNA59215-1425	209961	June 9, 1998
30	DNA59220-1514	209962	June 9, 1998
	DNA59488-1603	203157	August 25, 1998
	DNA59493-1420	203050	July 1, 1998
	DNA59497-1496	209941	June 4, 1998
	DNA59588-1571	203106	August 11, 1998
35	DNA59603-1419	209944	June 9, 1998
	DNA59605-1418	203005	June 23, 1998
	DNA59606-1471	209945	June 9, 1998
	DNA59607-1497	209957	June 9, 1998
	DNA59609-1470	209963	June 9, 1998
40	DNA59610-1559	209990	June 16, 1998
	DNA59612-1466	209947	June 9, 1998
	DNA59613-1417	203007	June 23, 1998
	DNA59616-1465	209991	June 16, 1998
	DNA59619-1464	203041	July 1, 1998
45	DNA59620-1463	209989	June 16, 1998
	DNA59625-1498	209992	June 17, 1998
	DNA59767-1489	203108	August 11, 1998
	DNA59776-1600	203128	August 18, 1998
	DNA59777-1480	203111	August 11, 1998
50	DNA59820-1549	203129	August 18, 1998
	DNA59827-1426	203089	August 4, 1998
	DNA59828-1608	203158	August 25, 1998
	DNA59838-1462	209976	June 16, 1998
	DNA59839-1461	209988	June 16, 1998
55	DNA59841-1460	203044	July 1, 1998
	DNA59842-1502	209982	June 16, 1998

	DNA59846-1503	209978	June 16, 1998
	DNA59847-1511	203098	August 4, 1998
	DNA59848-1512	203088	August 4, 1998
	DNA59849-1504	209986	June 16, 1998
	DNA59853-1505	209985	June 16, 1998
5	DNA59854-1459	209974	June 16, 1998
	DNA60283-1484	203043	July 1, 1998
	DNA60615-1483	209980	June 16, 1998
	DNA60619-1482	209993	June 16, 1998
	DNA60621-1516	203091	August 4, 1998
10	DNA60622-1525	203090	August 4, 1998
	DNA60625-1507	209975	June 16, 1998
	DNA60627-1508	203092	August 4, 1998
	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203112	August 11, 1998
15	DNA61873-1574	203132	August 18, 1998
	DNA62814-1521	203093	August 4, 1998
	DNA62872-1509	203100	August 4, 1998
	DNA62876-1517	203095	August 4, 1998
	DNA62881-1515	203096	August 4, 1998
20	DNA64852-1589	203127	August 18, 1998
	DNA64884-1527	203155	August 25, 1998
	DNA64890-1612	203131	August 18, 1998
	DNA65412-1523	203094	August 4, 1998
	DNA66308-1537	203159	August 25, 1998
25	DNA66309-1538	203235	September 15, 1998
	DNA67004-1614	203115	August 11, 1998
	DNA68869-1610	203164	August 25, 1998
	DNA68872-1620	203160	August 25, 1998
30	DNA71159-1617	203135	August 18, 1998

These deposit were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the

deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition
5 to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. Isolated nucleic acid having at least 80% sequence identity to a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ

ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422) and Figure 306 (SEQ ID NO:424).

2. The nucleic acid sequence of Claim 1, wherein said nucleotide sequence comprises a nucleotide
5 sequence selected from the group consisting of the sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72),
10 Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204),
15 Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288),
20 Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372),

Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) and Figure 305 (SEQ ID NO:423).

3. The nucleic acid of Claim 1, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of the full-length coding sequence of the sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID

NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) or Figure 305 (SEQ ID NO:423).

4. Isolated nucleic acid which comprises the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 2.

5. A vector comprising the nucleic acid of Claim 1.

6. The vector of Claim 5 operably linked to control sequences recognized by a host cell transformed with the vector.

7. A host cell comprising the vector of Claim 5.

8. The host cell of Claim 7 wherein said cell is a CHO cell.

9. The host cell of Claim 7 wherein said cell is an *E. coli*.

10. The host cell of Claim 7 wherein said cell is a yeast cell.

11. A process for producing a PRO polypeptides comprising culturing the host cell of Claim 7 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

12. Isolated PRO polypeptide having at least 80% sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68

(SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422) and Figure 306 (SEQ ID NO:424).

13. Isolated PRO polypeptide having at least 80% sequence identity to the amino acid sequence encoded by a nucleic acid molecule deposited under any ATCC accession number shown in Table 2.

14. A chimeric molecule comprising a polypeptide according to Claim 12 fused to a heterologous amino acid sequence.

15. The chimeric molecule of Claim 14 wherein said heterologous amino acid sequence is an epitope tag sequence.

16. The chimeric molecule of Claim 14 wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

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17. An antibody which specifically binds to a PRO polypeptide according to Claim 12.

18. The antibody of Claim 17 wherein said antibody is a monoclonal antibody.

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19. The antibody of Claim 17 wherein said antibody is a humanized antibody.

20. The antibody of Claim 17 wherein said antibody is an antibody fragment.

21. An isolated nucleic acid molecule which has at least 80% sequence identity to a nucleic acid which comprises a nucleotide sequence selected from the group consisting of that shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure

191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) and Figure 305 (SEQ ID NO:423).

22. An isolated nucleic acid molecule which has at least 80% sequence identity to the full-length coding sequence of a nucleotide sequence selected from the group consisting of that shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID

NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) and Figure 305 (SEQ ID NO:423).

- 20 23. An isolated extracellular domain of of PRO polypeptide.
24. An isolated PRO polypeptide lacking its associated signal peptide.
25. An isolated polypeptide having at least about 80% amino acid sequence identity to an
- 25 extracellular domain of of PRO polypeptide.
26. An isolated polypeptide having at least about 80% amino acid sequence identity to a PRO
- polypeptide lacking its associated signal peptide.

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FIGURE 1

CGGACGCGTGGGTGCGAGGCGAAGGTGACCGGGGACCGAGCATTTTCAGATCTGCTCGGTAGA
CCTGGTGCACCACCACCATGTTGGCTGCAAGGCTGGTGTGTCTCCGGACACTACCTTCTAGG
GTTTTCCACCCAGCTTTCACCAAGGCCTCCCCTGTTGTGAAGAATTCCATCACGAAGAATCA
ATGGCTGTTAACACCTAGCAGGGAATATGCCACCAAAAACAAGAATTGGGATCCGGCGTGGGA
GAACTGGCCAAGAAGCTCAAAGAGGCAGCATTGGAACCATCGATGGAAAAAATATTTAAAATT
GATCAGATGGGAAGATGGTTTGTGCTGGAGGGGCTGCTGTTGGTCTTGAGCATTGTGCTA
CTATGGCTTGGGACTGTCTAATGAGATTGGAGCTATTGAAAAGGCTGTAATTTGGCCTCAGT
ATGTCAAGGATAGAATTCATTCCACCTATATGTACTTAGCAGGGAGTATTGGTTTAACAGCT
TTGTCTGCCATAGCAATCAGCAGAACGCCTGTTCTCATGAACTTCATGATGAGAGGCTCTTG
GGTGACAATTGGTGTGACCTTTGCAGCCATGGTTGGAGCTGGAATGCTGGTACGATCAATAC
CATATGACCAGAGCCCAGGCCCAAAGCATCTTGCTTGGTTGCTACATTCTGGTGTGATGGGT
GCAGTGGTGGCTCCTCTGACAATATTAGGGGGTCCTCTTCTCATCAGAGCTGCATGGTACAC
AGCTGGCATTGTGGGAGGCCTCTCCACTGTGGCCATGTGTGCGCCCAGTGAAAAGTTTCTGA
ACATGGGTGCACCCCTGGGAGTGGGCCTGGGTCTCGTCTTTGTGTCCTCATTGGGATCTATG
TTTCTTCCACCTACCACCGTGGCTGGTGCCACTCTTTACTCAGTGGCAATGTACGGTGGATT
AGTTCTTTTCAGCATGTTCTTCTGTATGATACCCAGAAAGTAATCAAGCGTGCAGAAGTAT
CACCAATGTATGGAGTTCAAAAATATGATCCCATTAACTCGATGCTGAGTATCTACATGGAT
ACATTAAATATATTTATGCGAGTTGCAACTATGCTGGCAACTGGAGGCAACAGAAAGAAATG
AAGTGA~~CT~~CAGCTTCTGGCTTCTCTGCTACATCAAATATCTTGTTTAATGGGGCAGATATGC
ATTAAATAGTTTGTACAAGCAGCTTTCGTTGAAGTTTAGAAGATAAGAAACATGTCATCATA
TTTAAATGTTCCGGTAATGTGATGCCTCAGGTCTGCCTTTTTTTCTGGAGAATAAATGCAGT
AATCCTCTCCCAAATAAGCACACACATTTTCAATTCTCATGTTTGAGTGATTTTAAAATGTT
TTGGTGAATGTGAAAATAAGTTTGTGTCATGAGAATGTAAGTCTTTTTTCTACTTTAAAA
TTTAGTAGGTTCACTGAGTAACTAAAATTTAGCAAACCTGTGTTTGCATATTTTTTTGGAGT
GCAGAATATTGTAATTAATGTCATAAGTGATTTGGAGCTTTGGTAAAGGGACCAGAGAGAAG
GAGTCACCTGCAGTCTTTTGTTTTTTTAAATACTTAGAACTTAGCACTTGTGTTATTGATTA
GTGAGGAGCCAGTAAGAAACATCTGGGTATTTGGAAACAAGTGGTCATTGTTACATTCATTT
GCTGAACTTAACAAAAGTTCATCCTGAAACAGGCACAGGTGATGCATTCTCCTGCTGTTG
CTTCTCAGTGCTCTCTTTCCAATATAGATGTGGTCATGTTTGACTTGTACAGAATGTTAATC
ATACAGAGAATCCTTGATGGAATTATATATGTGTGTTTTACTTTTGAATGTTACAAAAGGAA
ATAACTTTAAAAGTATTCTCAAGAGAAAATATTCAAAGCATGAAATATGTTGCTTTTTCCAG
AATACAAACAGTATACTCATG

FIGURE 2

MLAARLVCLRTLPSRVFHPAFTKASPVVKNSITKNQWLLTPSREYATKTRIGIRRGRTGQEL
KEAALEPSMEKIFKIDQMGRWFVAGGAAVGLGALCYGLGLSNEIGAIEKAVIWPQYVKDRI
HSTYMYLAGSIGLTALSAIAISRTPVLMNFMMRGSWVTIGVTFAAMVGAGMLVRSIPYDQSP
GPKHLAWLLHSGVMGAVVAPLTILGGPLLIRAAWYTAGIVGGLSTVAMCAPSEKFLNMGAPL
GVGLGLVFVSSLGSMFLPPTTVAGATLYSVAMYGGLVLFMSMFLLYDTQKVIKRAEVSPMYGV
QKYDPINSMLSIYMDTLNIFMRVATMLATGGNRKK

FIGURE 3

GAAGGCTGCCTCGCTGGTCCGAATTCGGTGGCGCCACGTCCGCCCCTCTCCGCCTTCTGCAT
CGCGGCTTCGGCGGCTTCCACCTAGACACCTAACAGTCGCGGAGCCGGCCGCTCGTGAGGG
GGTCGGCACGGGGAGTCGGGCGGTCTTGTGCATCTTGGCTACCTGTGGGTCTGAAGATGTCGG
ACATCGGAGACTGGTTCAGGAGCATCCCGGCGATCACGCGCTATTGGTTCGCCGCCACCGTC
GCCGTGCCCTTGGTCCGCAAACTCGGCCTCATCAGCCCGGCTACCTCTTCTCTGGCCCGA
AGCCTTCTTTATCGCTTTCAGATTTGGAGGCCAATCACTGCCACCTTTTATTTCCCTGTGG
GTCCAGGAACTGGATTTCTTTATTTGGTCAATTTATATTTCTTATATCAGTATTCTACGCGA
CTTGAAACAGGAGCTTTTGATGGGAGGCCAGCAGACTATTTATTCATGCTCCTCTTTAACTG
GATTTGCATCGTGATTACTGGCTTAGCAATGGATATGCAGTTGCTGATGATTCTCTGATCA
TGTCAGTACTTTATGTCTGGGCCCAGCTGAACAGAGACATGATTGTATCATTTTGGTTTGGG
ACACGATTTAAGGCCTGCTATTTACCCTGGGTATCTTGGATTCAACTATATCATCGGAGG
CTCGGTAATCAATGAGCTTATTGGAAATCTGGTTGGACATCTTTATTTTTTCTAATGTTCA
GATACCAATGGACTTGGGAGGAAGAAATTTTCTATCCACACCTCAGTTTTTGTACCGCTGG
CTGCCCAGTAGGAGAGGAGGAGTATCAGGATTTGGTGTGCCCCCTGCTAGCATGAGGCGAGC
TGCTGATCAGAATGGCGGAGGCGGGAGACACAACCTGGGGCCAGGGCTTTCGACTTGGAGACC
AGTGAAGGGGCGGCCTCGGGCAGCCGCTCCTCTCAAGCCACATTTCTCTCCAGTGCTGGGTG
CACTTAACAACCTGCGTTCTGGCTAACACTGTTGGACCTGACCCACACTGAATGTAGTCTTTC
AGTACGAGACAAAGTTTCTTAAATCCCGAAGAAAAATATAAGTGTTCACAAGTTTTCACGAT
TCTCATTCAAGTCTTACTGCTGTGAAGAACAAATACCAACTGTGCAAAATGCAAACTGAC
TACATTTTGTGGTGTCTTCTCTTCCCTTTCCTGCTGAATAATGGGTTTATAGCGGGTCTCT
AATCTGTCTGGCATTGAGCTGGGGCTGGGTACCAAACCCCTTCCCAAAGGACCTTATCTCTT
TCTTGCACACATGCCTCTCTCCCACTTTTCCCAACCCCCACATTTGCAACTAGAAAAAGTTG
CCCATAAAATTGCTCTGCCCTTGACAGGTTCTGTTATTTATTGACTTTTGCCAAGGCTGGTC
ACAACAATCATATTCACGTTATTTTCCCCTTTTGGTGGCAGAACTGTTACCAATAGGGGGAG
AAGACAGCCACGGATGAAGCGTTTCTCAGCTTTTGGAAATTGCTTCGACTGACATCCGTTGTT
AACCCTTTGCCACTCTTCAGATATTTTATAAAAAAGTACCACTGAGTTCATGAGGGCCA
CAGATTGGTTATTAATGAGATACGAGGGTGGTGCTGGGTGTTTGTTCCTGAGCTAAGTGA
TCAAGACTGTAGTGGAGTTGCAGCTAACATGGGTTAGGTTTAAACCATGGGGGATGCACCCC
TTTGCCTTTCATATGTAGCCCTACTGGCTTTGTGTAGCTGGAGTAGTTGGGTTGCTTGTGT
TAGGAGGATCCAGATCATGTTGGCTACAGGGAGATGCTCTCTTGGAGAGGTCTGGGCATTG
ATTCCCATTTCAATCTCATTCTGGATATGTGTTCAATTGAGTAAAGGAGGAGAGACCCTCATA
CGCTATTTAAATGTCACTTTTTTGCCTATCCCCCGTTTTTTGGTCATGTTTCAATTAATTGT
GAGGAAGGCGCAGCTCCTCTCTGCACGTAGATCATTTTTTAAAGCTAATGTAAGCACATCTA
AGGGAATAACATGATTTAAGGTTGAAATGGCTTTAGAATCATTTGGGTTTGAGGGTGTGTTA
TTTTGAGTCATGAATGTACAAGCTCTGTGAATCAGACCAGCTTAAATACCCACACCTTTTTT
TCGTAGGTGGGCTTTTCTATCAGAGCTTGGCTCATAACCAAATAAAGTTTTTTGAAGGCCA
TGGCTTTTACACAGTTATTTTATTTATGACGTTATCTGAAAGCAGACTGTTAGGAGCAGT
ATTGAGTGGCTGTACACTTTGAGGCAACTAAAAAGGCTTCAAACGTTTTGATCAGTTTCTT
TTCAGGAAACATTGTGCTCTAACAGTATGACTATTCTTTCCCCCACTCTTAAACAGTGTGAT
GTGTGTTATCCTAGGAAATGAGAGTTGGCAAACAACCTTCTCATTTTGAATAGAGTTTGTGTG
TACTTCTCCATATTTAATTTATATGATAAAATAGGTGGGGAGAGTCTGAACCTTAACTGTCA
TGTTTTGTGTTTATCTGTGGCCACAATAAAGTTTACTTGTAAAATTTTAGAGGCCATTACT
CCAATTATGTTGCACGTACACTCATTGTACAGGCGTGGAGACTCATTGTATGTATAAGAATA
TTTCTGACAGTGAGTGACCCGGAGTCTCTGGTGTACCCTCTTACCAGTCAGCTGCCTGCGAG
CAGTCATTTTTTCTAAAGGTTTACAAGTATTTAGAAGTTTTTCTAGTTCAGGGCAAAATGTTT
ATGAAGTTATTCCTCTTAAACATGGTTAGGAAGCTGATGACGTTATTGATTTTGTCTGGATT
ATGTTTCTGGAATAATTTTACCAAACAAGCTATTTGAGTTTTGACTTGACAAGGCAAAACA
TGACAGTGGATTCTCTTTACAAATGGAAAAAAAATCCTTATTTTGTATAAAGGACTTCCC
TTTTTGTAACTAATCCTTTTTATTGGTAAAAATGTAAATTAAATGTGCAACTTG

FIGURE 4

MSDIGDWFRSIPAITRYWFAATVAVPLVGKLGLISPAYLFLWPEAFLYRFQIWRPITATFYF
PVGPGTGFLYLVNLYFLYQYSTRLETGAFDGRPADYLFMLLFNWICIVITGLAMDMQLLMIP
LIMSVLYVWAQLNRDMIVSFWFGTRFKACYLPWVILGFNYIIIGGSVINELIGNLVGHLYFFL
MFRYPMDLGGRNFLSTPQFLYRWLPSRRGGVSGFGVPPASMRRAADQNGGGGRHNWGQGFRLGDQ

FIGURE 5

GGGGCCGCGGTCTAGGGCGGCTACGTGTGTTGCCATAGCGACCATTTTGCATTAAGTGGTTG
GTAGCTTCTATCCTGGGGGCTGAGCGACTGCGGGCCAGCTCTTCCCCTACTCCCTCTCGGCT
CCTTGTGGCCCAAAGGCCTAACCGGGGTCCGGCGGTCTGGCCTAGGGATCTTCCCCGTTGCC
CCTTTGGGGCGGGATGGCTGCGGAAGAAGAAGACGAGGTGGAGTGGGTAGTGGAGAGCATCG
CGGGGTTCTGCGAGGCCCAGACTGGTCCATCCCCATCTTGGACTTTGTGGAACAGAAATGT
GAAGTTAACTGCAAAGGAGGGCATGTGATAACTCCAGGAAGCCCAGAGCCGGTGATTTTGGT
GGCCTGTGTTCCCCTTGTTTTTGATGATGAAGAAGAAAGCAAATTGACCTATACAGAGATTC
ATCAGGAATACAAAGAACTAGTTGAAAAGCTGTTAGAAGGTTACCTCAAAGAAATTGGAATT
AATGAAGATCAATTTCAAGAAGCATGCACCTTCTCCTCTTGCAAAGACCCATACATCACAGGC
CATTTTGCAACCTGTGTTGGCAGCAGAAGATTTTACTATCTTTAAAGCAATGATGGTCCAGA
AAAACATTGAAATGCAGCTGCAAGCCATTGCAATAATTCAAGAGAGAAATGGTGTATTACCT
GACTGCTTAACCGATGGCTCTGATGTGGTCAGTGACCTTGAACACGAAGAGATGAAAATCCT
GAGGGAAGTTCTTAGAAAATCAAAGAGGAATATGACCAGGAAGAAGAAAGGAAGAGGAAAA
AACAGTTATCAGAGGCTAAAACAGAAGAGCCACAGTGCATTCCAGTGAAGCTGCAATAATG
AATAATTCCCAAGGGGATGGTGAACATTTTGCACACCCACCCTCAGAAGTTAAAATGCATTT
TGCTAATCAGTCAATAGAACCTTTGGGAAGAAAAGTGGAAAGGTCTGAACTTCCTCCCTCC
CACAAAAGGCCTGAAGATTCCTGGCTTAGAGCATGCGAGCATTGAAGGACCAATAGCAAAC
TTATCAGTACTTGGAACAGAAGAACTTCGGCAACGAGAACACTATCTCAAGCAGAAGAGAGA
TAAGTTGATGTCCATGAGAAAGGATATGAGGACTAAACAGATACAAAATATGGAGCAGAAAG
GAAAACCCACTGGGGAGGTAGAGGAAATGACAGAGAAACCAGAAATGACAGCAGAGGAGAAG
CAAACATTACTAAAGAGGAGATTGCTTGCAAGAGAACTCAAAGAAGAAGTTATTAATAAGTA
ATAATTAAGAACAATTTAACAAAATGGAAGTTCAAATTGTCTTAAAAATAAATTATTTAGTC
CTTACACTG

FIGURE 6

MAAEEDEVEWVVESIAGFLRGPDWSIPILDFVEQKCEVNCKGGHVITPGSPEPVILVACVP
LVFDDEESKLTYTEIHQEYKELVEKLLEGYLKEIGINEDQFQEACTSPLAKTHTSQAILQP
VLAAEDFTIFKAMMVQKNIEMQLQAIRIIQERNGLVPDCLTDGSDVVSLEHEEMKILREVL
RKSKEEYDQEEERKRKKQLSEAKTEEPTVHSSEAAIMNNSQGDGEHFAHPPSEVKMHFANQS
IEPLGRKVERSETSSLPQKGLKIPGLEHASIEGPANLSVLGTEELRQREHYLKQKRDKLMS
MRKDMRTKQIQNMEQKGKPTGEVEEMTEKPEMTAEEKQTLLKRLLAEKLKEEVINK

FIGURE 7

GGGCACAGCACATGTGAAGTTTTTGATGATGAAGAAGAAAGCAAATTGACCTATACAGAGAT
TCATCAGGAATACAAAGAAGCTAGTTGAAAAGCTGTTAGAAGGTTACCTCAAAGAAATTGGAA
TTAATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGCAAAGACCCATACATCACAG
GCCATTTTTGCAACCTGTGTTGGCAGCAGAAGATTTTACTATCTTTAAAGCAATGATGGTCC
AGAAAAACATTGAAATGCAGCTGCAAGCCATTGCAATAATTCAAGAGAGAAATGGTGTATTA
CCTGACTGCTTAACCGATGGCTCTGATGTGGTCAGTGACCTTGAACACGAAGAGATGAAAAT
CCTGAGGGAAGTTCTTAGAAAATCAAAAGAGGAATATGACCAGGAA

FIGURE 8

GCGTGGTTTTTGTCTGCAATAGGCGGCTTAGAGGGAGGGGCTTTTTCGCCTATACCTACTG
TAGCTTCTCCACGTATGGACCCTAAAGGCTACTGCTGCTACTACGGGGCTAGACAGTTACTG
TCTCAGCTCTAGGATGTGCGTTCTTCCACTAGAAGCTCTTCTGAGGGAGGTAATTAACAAAC
AGTGGAAATGGAAAAACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCACAATGTATAC
ATTCTGCTAGGTGCCATATTCATTGCTTTAAGCTCAAGTCGCATCTTACTAGTGAAGTATT
CTGCCAATGAAGAAAAACAGTATGATTATCTTCCAACACTGTGAATGTGTGCTCAGAACTG
GTGAAGCTAGTTTTCTGTGTGCTTGTGTCAATTCTGTGTTATAAAGAAAGATCATCAAAGTAG
AAATTTGAAATATGCTTCCTGGAAGGAATTCTCTGATTTTCATGAAGTGGTCCATTCTGCCT
TTCTTTATTTCTGGAATACTTGATTGTCTTCTATGTCTCTGCTATCTTCAACCAGCCATG
GCTGTTATCTTCTCAAATTTTAGCATTATAACAACAGCTCTTCTATTCAAGGATAGTGCTGAA
GAGGCGTCTAAACTGGATCCAGTGGGCTTCCCTCCTGACTTTATTTTTGTCTATTGTGGCCT
TGACTGCCGGGACTAAACTTTACAGCACAACCTGGCAGGACGTGGATTTTCATCACGATGCC
TTTTTCAGCCCTTCCAATTCCTGCCTTCTTTTCAGAAGTGAGTGTCCCAGAAAAGACAATTG
TACAGCAAAGGAATGGACTTTTCTGAAGCTAAATGGAACACCACAGCCAGAGTTTTTCAGTC
ACATCCGTCTTGGCATGGGCCATGTTCTTATTATAGTCCAGTGTTTTTATTCTTCAATGGCT
AATATCTATAATGAAAAGATACTGAAGGAGGGGAACCAGCTCACTGAAAGCATCTTCATACA
GAACAGCAAACCTCTATTTCTTTGGCATTCTGTTTAATGGGCTGACTCTGGGCCTTCAGAGGA
GTAACCGTGATCAGATTAAGAACTGTGGATTTTTTTATGGCCACAGTGCATTTTCAGTAGCC
CTTATTTTTGTAACTGCATTCCAGGGCCTTTTCAGTGGCTTTTCATTCTGAAGTTCCTGGATAA
CATGTTCCATGTCTTGATGGCCCAGGTTACCACTGTCAATTATCACAAACAGTGTCTGTCTGG
TCTTTGACTTCAGGCCCTCCCTGGAATTTTTCTTGAAGCCCCATCAGTCCTTCTCTCTATA
TTTATTTATAATGCCAGCAAGCCTCAAGTTCGGGAATACGCACCTAGGCAAGAAAGGATCCG
AGATCTAAGTGGCAATCTTTGGGAGCGTTCCAGTGGGGATGGAGAAGAACTAGAAAGACTTA
CCAAACCCAAGAGTGATGAGTCAGATGAAGATACTTTCTAACTGGTACCCACATAGTTTGCA
GCTCTCTTGAACCTTATTTTCACATTTTCAGTGTGTGTAATATTTATCTTTTCACTTTGATA
AACCAGAAATGTTTCTAAATCCTAATATTCTTTGCATATATCTAGCTACTCCCTAAATGGTT
CCATCCAAGGCTTAGAGTACCCAAAGGCTAAGAAATTCTAAAGAACTGATACAGGAGTAACA
ATATGAAGAATTCATTAATATCTCAGTACTTGATAAATCAGAAAGTTATATGTGCAGATTAT
TTTCTTGGCCTTCAAGCTTCCAAAAAAGCTTGTAATAATCATGTTAGCTATAGCTTGATAT
ACACATAGAGATCAATTTGCCAAATATTACAATCATGTAGTTCTAGTTTACATGCCAAAGT
CTTCCCTTTTTTAACATTATAAAAGCTAGGTTGTCTCTTGAATTTTGAGGCCCTAGAGATAGT
CATTTTGCAAGTAAAGAGCAACGGGACCCTTTCTAAAAACGTTGGTTGAAGGACCTAAATAC
CTGGCCATACCATAGATTTGGGATGATGTAGTCTGTGCTAAATATTTTGCTGAAGAAGCAGT
TTCTCAGACACAACATCTCAGAATTTTAATTTTTAGAAATTCATGGGAAATTGGATTTTTGT
AATAATCTTTTGATGTTTTAAACATTGGTTCCCTAGTCACCATAGTTACCACTTGTATTTTA
AGTCATTTAAACAAGCCACGGTGGGGCTTTTTCTCCTCAGTTTGAGGAGAAAAATCTTGAT
GTCATTACTCCTGAATTATTACATTTTGGAGAATAAGAGGGCATTTTATTTTATTAGTTACT
AATTCAGCTGTGACTATTGTATATCTTTCCAAGAGTTGAAATGCTGGCTTCAGAATCATAC
CAGATTGTGCTGAGTGAAGCTGATGCCTAGGAACCTTTTAAAGGGATCCTTTCAAAGGATCACTT
AGCAAACACATGTTGACTTTTAACTGATGTATGAATATTAATACTCTAAAAATAGAAAGACC
AGTAATATATAAGTCACTTTACAGTGCTACTTCACACTTAAAAGTGCATGGTATTTTTCATG
GTATTTTGCATGCAGCCAGTTAACTCTCGTAGATAGAGAAGTCAGGTGATAGATGATATTAA
AAATTAGCAAACAAAAGTGACTTGCTCAGGGTCATGCAGCTGGGTGATGATAGAAGAGTGGG
CTTTAACTGGCAGGCCTGTATGTTTACAGACTACCATACTGTAAATATGAGCTTTATGGTGT
CATTTCTCAGAACTTATACATTTCTGCTCTCCTTTCTCCTAAGTTTCATGCAGATGAATATA
AGGTAATATACTATTATATAATTCATTTGTGATATCCACAATAATATGACTGGCAAGAATTG
GTGGAAATTTGTAATTAAAATAATTATTAAACCT

FIGURE 9

MEKQCCSHPVICSLSTMYTFLLGAIFIALSSSRILLVKYSANEENKYDYLPTTVNVCSELVK
LVFCVLVSFCVIKKDHQSRNLKYASWKEFSDFMKWSIPAFLYFLDNLIVFYVLSYLQPAMAV
IFSNFSIITTALLFRIVLKRRLNWIQWASLLTLFLSIVALTAGTKTLQHNLAGRGFHHDAFF
SPSNSCLLFRSECPRKDNCTAKEWTFPEAKWNTTARVFSHIRLGMGHVLIIVQCFISSMANI
YNEKILKEGNQLTESIFIQNSKLYFFGILFNGLTLGLQRSNRDQIKNCGFFYGHSAFSVALI
FVTAFQGLSVAFILKFLDNMFHVLMAQVTTVIITTVSVLVFDFRPSLEFFLEAPSVLLSIFI
YNASKPQVPEYAPRQERIRDLSGNLWERSSSGDGEELERLTKPKSDESDETF

FIGURE 10

CGTGCCTGCGCAATGGGTGTCGGGTCCGCTTTTTCCCAATCCGGACGTAATCGTGGTTTTTG
TTCTGCAATAGGCGGCTTAGAGGGAGGGGCTTTTTCGCCTATACCTACTGTAGCTTCTCCAC
GTATGGACCCTAAAGGCTACTGCTGCTACTACGGGGCTAGACAGTTACTGTCTCAGCTCTAG
GATGTGCGTTCTTCCACTAGAAGCTCTTCTGAGGGAGGTAATTAAAAAACAGTGGAATGGAA
AAACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCACAATGTATACATTCTGCTAGG
TGCCATATTCATTGCTTTAAGCTCAAGTCGCATCTTACTAGTGAAGTATTCTGCCAATGAAG
AAAACAAGTATGATTATCTTCCAACACTGTGAATGTGTGCTCAGAACTGGTGAAGCTAGTT
TTCTGTGTGCTTGTGTCAATTCTGTGTTATAAAGAAAGATCATCAAAGTAGAAATTTGAAATA
TGCTTCCTGGAAGGAATTCTCTGATTTTCATGAAGTGGTCCATTCCTGCCTTTCTTTATTTCC
TGGATAACTTGATTGTCTTCTATGTCCTGTCCTATCTTCAACCAGCCATGGCTGTTATCTTC
TCAAATTTTAGCATTATAACAACAGCTCTTCTATTTCAGGATAGTGCTGAAGAGGCGTCTAAA
CTGGATCCAGTGGGCTTCCCTCCTGACTTTATTTTTGTCTATTGTGGCCTTGACTGCCGGGA
CTAAAACTTTA

FIGURE 11

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGGCCGGCTTGGCTAGCGCGCGGCGGCC
GTGGCTAAGGCTGCTACGAAGCGAGCTTGGGAGGAGCAGCGGCCTGCGGGGCAGAGGAGCAT
CCCGTCTACCAGGTCCCAAGCGGCGTGGCCCGCGGGTCATGGCCAAAGGAGAAGGCGCCGAG
AGCGGCTCCGCGGCGGGCTGCTACCCACCAGCATCCTCCAAAGCACTGAACGCCCGGCCCA
GGTGAAGAAAGAACC GAAAAAGAAGAAACAACAGTTGTCTGTTTGCAACAAGCTTTGCTATG
CACTTGGGGGAGCCCCCTACCAGGTGACGGGCTGTGCCCTGGGTTTCTTCCTTCAGATCTAC
CTATTGGATGTGGCTCAGGTGGGCCCTTTCTCTGCCTCCATCATCCTGTTTGTGGGCGGAGC
CTGGGATGCCATCACAGACCCCCTGGTGGGCCTCTGCATCAGCAAATCCCCCTGGACCTGCC
TGGGTGCGCTTATGCCCTGGATCATCTTCTCCACGCCCTGGCCGTCATTGCCTACTTCCTC
ATCTGGTTCGTGCCCGACTTCCACACGGCCAGACCTATTGGTACCTGCTTTTCTATTGCCT
CTTTGAAACAATGGTCAAGTGTTCATGTTCCCTACTCGGCTCTCACCATGTTTCATCAGCA
ACCGAGCAGACTGAGCGGGATTCTGCCACCGCCTATCGGATGACTGTGGAAGTGCTGGGCAC
AGTGCTGGGCACGGCGATCCAGGGACAAATCGTGGGCCAAGCAGACACGCCTTGTTTCCAGG
ACTTCAATAGCTCTACAGTAGCTTCACAAAGTGCCAACCATAACATGGCACCACCTTCACAC
AGGGAAACGCAAAGGCATACCTGCTGGCAGCGGGGTCATTGTCTGTATCTATATAATCTG
TGCTGTATCCTGATCCTGGGCGTGCGGGAGCAGAGAGAACCCTATGAAGCCCAGCAGTCTG
AGCCAATCGCCTACTTCCGGGGCCTACGGCTGGTTCATGAGCCACGGCCCATAACATCAAACCT
ATTACTGGCTTCCTCTTCACCTCCTTGGCTTTTCATGCTGGTGGAGGGAACTTTGTCTTGTT
TTGCACCTACACCTTGGGCTTCCGCAATGAATTCAGAATCTACTCCTGGCCATCATGCTCT
CGGCCACTTTAACCATTCCCATCTGGCAGTGGTTCTTGACCCGGTTTGGCAAGAAGACAGCT
GTATATGTTGGGATCTCATCAGCAGTGCCATTTCTCATCTTGGTGGCCCTCATGGAGAGTAA
CCTCATCATTACATATGCGGTAGCTGTGGCAGCTGGCATCAGTGTGGCAGCTGCCTTCTTAC
TACCCTGGTCCATGCTGCCTGATGTGCTTGCAGACTTCCATCTGAAGCAGCCCCACTTCCAT
GGAACCGAGCCCATCTTCTTCTCCTTCTATGTCTTCTTACCAAGTTTGCCTCTGGAGTGTC
ACTGGGCATTTCTACCCCTCAGTCTGGACTTTGCAGGGTACCAGACCCGTGGCTGCTCGCAGC
CGGAACGTGTCAAGTTTACACTGAACATGCTCGTGACCATGGCTCCCATAGTTCTCATCCTG
CTGGGCCTGCTGCTCTTCAAATGTACCCCATTTGATGAGGAGAGGCGGCGGCAGAATAAGAA
GGCCCTGCAGGCACTGAGGGACGAGGCCAGCAGCTCTGGCTGCTCAGAAACAGACTCCACAG
AGCTGGCTAGCATCCTCTAGGGCCCGCCACGTTGCCCCGAAGCCACCATGCAGAAGGCCACAG
AAGGGATCAGGACCTGTCTGCCGGCTTGCTGAGCAGCTGGACTGCAGGTGCTAGGAAGGGAA
CTGAAGACTCAAGGAGGTGGCCAGGACACTTGCTGTGCTCACTGTGGGGCCGGCTGCTCTG
TGGCCTCCTGCCTCCCCTCTGCCTGCCTGTGGGGCCAAGCCCTGGGGCTGCCACTGTGAATA
TGCCAAGGACTGATCGGGCCTAGCCCGGAACACTAATGTAGAAACCTTTTTTTTACAGAGCC
TAATTAATAACTTAATGACTGTGTACATAGCAATGTGTGTGTATGTATATGTCTGTGAGCTA
TTAATGTTATTAATTTTCATAAAAGCTGGAAAGC

FIGURE 12

MWLRWALS LPPSSCLWAEPGMPSQTPWWASASANPPGPAWVALCPGSSSPRPWPSLPTSSSG
SCPTSHTARPIGTCFSIASLKQWSRVSMFPTRLSPCSSATEQTERDSATAYRMTVEVLGTVL
GTAIQGQIVGQADTPCFQDFNSSTVASQSANHHTGTTSHRETQKAYLLAAGVIVCIYIICAV
ILILGVREQREPYEAAQSEPIAYFRGLRLVMSHGPYIKLITGFLFTSLAFMLVEGNFVLFCT
YTLGFRNEFQNL LLAIMLSATLTIPWQWFLTRFGKKTAVYVGISSAVPFLILVALMESNLI
ITYAVAVAAGISVAAAFLLPWSMLPDVIDDFHLKQPHFHGTEPIFFSFYVFFTKFASGVSLG
ISTLSLDFAGYQTRGCSQPERVKFTLNMLVTMAPIVLILLGLLLFKMYPIDEERRRQNKAL
QALRDEASSSGCSETDSTELASIL

FIGURE 13

GGGAAACGCAAAGGCATACCTGCTGGCAGCGGGGGTCATTGTCTGTATCTATATAATCTGT
GCTGTCATCCTGATCCTGGGCGTGCGGGAGCAGAGAGAACCCTATGAAGCCCAGCAGTCTGA
GCCAATCGCCTACTTCCGGGGCCTACGGCTGGTCATGAGCCACGGCCCATACATCAAACCTTA
TTACTGGCTTCCTCTTCACCTCCTTGGCTTTCATGCTGGTGGAGGGGAACCTTGTCTTGTTT
TGCACCTACACCTTGGGCTTCCGCAATGAATTCCAGAATCTACTCCTGGCCATCATGCTCTC
GGCCACTTTAACCATTCCCATCTGGCAGTGGTTCTTGACCCGGTTTGGCAAGAAGACAGCTG
TATATGTTGGGATCTCATCAGCAGTGCCATTTCTCATCTTGGTGGCCCTCATGGAGAGTAAC
CTCATCATTACATATGCGGTAGCTGTGGCAGCTGGCATCAGTGTGGCAGCTGCCTTCTTACT
ACCCTGGTCCATGCTGCCTGATGTCATTGACGACTTCCATCTGAAGCAGCCCCACTTCCATG
GAACCGAGCCCAT

FIGURE 14

GGGGCTTCGGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGGATTTACAAAAGGTGCAGGT
ATGAGCAGGTCTGAAGACTAACATTTTGTGAAGTTGTAAACAGAAAACCTGTTAGAAATGT
GGTGGTTTCAGCAAGGCCTCAGTTTCCTTCCTTCAGCCCTTGTAATTTGGACATCTGCTGCT
TTCATATTTTCATACATTACTGCAGTAACACTCCACCATATAGACCCGGCTTTACCTTATAT
CAGTGACACTGGTACAGTAGCTCCAGAAAAATGCTTATTTGGGGCAATGCTAAATATTGCGG
CAGTTTTATGCATTGCTACCATTTATGTTTCGTTATAAGCAAGTTCATGCTCTGAGTCCTGAA
GAGAACGTTATCATCAAATTAAACAAGGCTGGCCTTGTAAGTCTGGAATACTGAGTTGTTTAGG
ACTTTCTATTGTGGCAAACCTTCAGAAAAACAACCCCTTTTTGCTGCACATGTAAGTGGAGCTG
TGCTTACCTTTGGTATGGGCTCATTATATATGTTTGTTCAGACCATCCTTTTCTACCAAATG
CAGCCCCAAATCCATGGCAAACAAGTCTTCTGGATCAGACTGTTGTTGGTTATCTGGTGTGG
AGTAAGTGCACCTTAGCATGCTGACTTGCTCATCAGTTTTGCACAGTGGCAATTTTGGGACTG
ATTTAGAACAGAACTCCATTGGAACCCCGAGGACAAAGGTTATGTGCTTCACATGATCACT
ACTGCAGCAGAATGGTCTATGTCATTTTCCTTCTTTGGTTTTTTTCTGACTTACATTCGTGA
TTTTTCAGAAAATTTCTTTACGGGTGGAAGCCAATTTACATGGATTAACCCTCTATGACACTG
CACCTTGCCCTATTAACAATGAACGAACACGGCTACTTTCAGAGATATTTGATGAAAGGAT
AAAATATTTCTGTAATGATTATGATTCTCAGGGATTGGGGAAAGGTTACAGAAAGTTGCTTA
TTCTTCTCTGAAATTTTCAACCACTTAATCAAGGCTGACAGTAACACTGATGAATGCTGATA
ATCAGGAAACATGAAAGAAGCCATTTGATAGATTATTCTAAAGGATATCATCAAGAAGACTA
TTAAAAACACCTATGCCTATACTTTTTTATCTCAGAAAATAAAGTCAAAGACTATG

FIGURE 15

MWWFQQGLSFLPSALVIWTSAAFIYSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNI
AAVLCIATIIYVRYKQVHALSPEENVIIKLNKAGLVLGILSCLGLSIVANFQKTTLFAAHVSG
AVLTFGMGSLYMFVQTILSYQMOPKIHGKQVFWIRLLLVIWCGVSALSMLTCSSVLHSGNFG
TDLEQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGFFLTYYIRDFQKISLRVEANLHGLTLYD
TAPCPINNERTRLLSRDI

FIGURE 16

CGGACGCTTGGGCNGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGTGCCTGATGCCGAGT
TCCGTCTCTCGGGTCTTTTCCTGGTCCCAGGCAAAGCGGAGCGGAGATCCTCAAACGGCCTA
GTGCTTCGCGCTTCCGGAGAAAATCAGCGGTCTAATTAATTCCTCTGGTTTGTTGAAGCAGT
TACCAAGAATCTTCAACCCTTTCCACAAAAGCTAATTGAGTACACGTTCCCTGTTGAGTACA
CGTTCCTGTTGATTTACAAAAGGTGCAGGTATGAGCAGGTCTGAAGACTAACATTTTGTGAA
GTTGTAAAACAGAAAACCTGTTAGAAATGTGGTGGTTTCAGCAAGGCCTCAGTTTCCTTCCT
TCAGCCCTTGTAATTTGGACATCTGCTGCTTTCATATTTTCATACATTACTGCAGTAACACT
CCACCATATAGACCCGGCTTTACCTTATATCAGTGACACTGGTACAGTANC

FIGURE 17

CCCACGCGTCCGCCCCGCGCTGCGTCCCGGAGTGCAAGTGAGCTTCTCGGCTGCCCCGCGGG
CCGGGGTGCGGAGCCGACCATGCGCCCGCTTCTCGGCCTCCTTCTGGTCTTCGCCGGCTGCAC
CTTCGCCTTGTA~~CT~~TGCTGTGACGCGACTGCCCCGCGGGCGGAGACTGGGCTCCACCGAGG
AGGCTGGAGGCAGGTGCGTGTGGTTCCCCTCCGACCTGGCAGAGCTGCGGGAGCTCTCTGAG
GTCCTTCGAGAGTACCGGAAGGAGCACCAGGCCTACGTGTTCTTGCTCTTCTGCGGCGCCTA
CCTCTACAAACAGGGCTTTGCCATCCCCGGCTCCAGCTTCCTGAATGTTTTAGCTGGTGCCT
TGTTTGGGCCATGGCTGGGGCTTCTGCTGTGCTGTGTGTTGACCTCGGTGGGTGCCACATGC
TGCTACCTGCTCTCCAGTATTTTTGGCAAACAGTTGGTGGTGTCTACTTTTCTGATAAAGT
GGCCCTGCTGCAGAGAAAGGTGGAGGAGAACAGAAACAGCTTGTTTTTTTTCTTATTGTTTT
TGAGACTTTTCCCCATGACACCAA~~ACT~~GGTTCTTGAACCTCTCGGCCCCAATTCTGAACATT
CCCATCGTGCAGTTCTTCTTCTCAGTTCTTATCGGTTTGATCCCATATAATTTTCATCTGTGT
GCAGACAGGGTCCATCCTGTCAACCCTAACCTCTCTGGATGCTCTTTTCTCCTGGGACACTG
TCTTTAAGCTGTTGGCCATTGCCATGGTGGCATTAAATTCCTGGAACCCTCATTAAAAAATTT
AGTCAGAAACATCTGCAATTGAATGAAACAAGTACTGCTAATCATATACACAGTAGAAAAGA
CACATGATCTGGATTTTCTGTTTGCCACATCCCTGGACTCAGTTGCTTATTTGTGTAATGGA
TGTGGTCCTCTAAAGCCCCCTCATTGTTTTTGATTGCCTTCTATAGGTGATGTGGACACTGTG
CATCAATGTGCAGTGTCTTTTCAGAAAGGACACTCTGCTCTTGAAGGTGTATTACATCAGGT
TTTCAAACCAGCCCTGGTGTAGCAGACACTGCAACAGATGCCTCCTAGAAAATGCTGTTTGT
GGCCGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCCGGTGATTC
ACAAGGTCAGGAGTTCAAGACCAGCCTGGCCAAGATGGTGAAATCCTGTCTCTAATAAAAAAT
ACAAAAATTAGCCAGGCGTGGTGGCAGGCACCTGTAATCCCAGCTACTCGGGAGGCTGAGGC
AGGAGAATTGCTTGAACCAAGGTGGCAGAGGTTGCAGTAAGCCAAGATCACACCACTGCACT
CCAGCCTGGGTGATAGAGTGAGACACTGTCTTGAC

FIGURE 18

MRPLLGLLLVFAGCTFALYLLSTRLPGRRLGSTEEAGGRSLWFPSDLAELRESEVLREYR
KEHQAYVFLLEFCGAYLYKQGFAIPGSSFLNVLAGALFGPWLGLLLCCVLTSVGATCCYLLSS
IFGKQLVVSYPDKVALLQRKVEENRNSLFFLLFLRLFPMTPNWFLNLSAPILNIPIVQFF
FSVLIGLIPYNFICVQTGSILSTLTSLDALFSWDTVFKLLAIAMVALIPGTLIKKFSQKHLQ
LNETSTANHIHSRKDT

FIGURE 19

CCGAGGCGGGAGGAGCCCGAGGGGGCGCGAGCCCCGCATGAATCATTGTAGTCAATCATTTT
CCAGTTCTCAGCCGCTCAGTTGTGATCAAGGGACACGTGGTTTCCGAACTGCCAGCTCAGAA
TAGGAAAATAACTTGGGATTTTATATTGGAAGACATGGATCTTGCTGCCAACGAGATCAGCA
TTTATGACAACTTTCAGAGACTGTTGATTTGGTGAGACAGACCGGCCATCAGTGTGGCATG
TCAGAGAAGGCAATTGAAAAATTTATCAGACAGCTGCTGGAAAAGAATGAACCTCAGAGACC
CCCCCGCAGTATCCTCTCCTTATAGTTGTGTATAAGGTTCTCGCAACCTTGGGATTAATCT
TGCTCACTGCCTACTTTGTGATTCAACCTTTCAGCCCATTAGCACCTGAGCCAGTGCTTTCT
GGAGCTCACACCTGGCGCTCACTCATCCATCACATTAGGCTGATGTCCTTGCCCATTGCCAA
GAAGTACATGTCAGAAAATAAGGGAGTTCCTCTGCATGGGGGTGATGAAGACAGACCCTTTC
CAGACTTTGACCCCTGGTGGACAAACGACTGTGAGCAGAATGAGTCAGAGCCCATTCTGCC
AACTGCACTGGCTGTGCCCAGAAACACCTGAAGGTGATGCTCCTGGAAGACGCCCCAAGGAA
ATTTGAGAGGCTCCATCCACTGGTGATCAAGACGGGAAAGCCCCTGTTGGAGGAAGAGATTC
AGCATTTTTTGTGCCAGTACCCTGAGGCGACAGAAGGCTTCTCTGAAGGGTTTTTCGCCAAG
TGGTGGCGCTGCTTTCCTGAGCGGTGGTTCCCATTTCTTATCCATGGAGGAGACCTCTGAA
CAGATCACAAATGTTACGTGAGCTTTTTCTGTCTTTCACTCACCTGCCATTTCCAAAAGATG
CCTCTTTAAACAAGTGCTCCTTTCTTCACCCAGAACCTGTTGTGGGGAGTAAGATGCATAAG
ATGCCTGACCTATTTATCATTGGCAGCGGTGAGGCCATGTTGCAGCTCATCCCTCCCTTCCA
GTGCCGAAGACATTGTCACTGTGGCCATGCCAATAGAGCCAGGGGATATCGGCTATGTCTG
ACACCACCCACTGGAAGGTCTACGTTATAGCCAGAGGGGTCCAGCCTTTGGTCATCTGCGAT
GGAACCGCTTTCTCAGAACTGTAGGAAATAGAACTGTGCACAGGAACAGCTTCAGAGCCGA
AAACCAGGTTGAAAGGGGAAAAATAAAAACAAAAACGATGAAACTGCAAAAA

FIGURE 20

MDLAANEISIIYDKLSETVDLVRQTGHQCGMSEKAIEKFIRQLLEKNEPQRPPQYPLLIVVY
KVLATLGLILLTAYFVIQPFSPLAPEPVLSGAHTWRS LIHHIRLMSLP IAKKYMSENKGVPL
HGGDEDRPFPDFDPWWTNDCEQNESEPI PANCTGCAQKHLKVMLLEDAPRKFERLHPLVIKT
GKPLLEEEIQHFLCQYPEATEGFSEGGFAKWWRCFPERWFPPYPWRRPLNRSQMLRELFV
FTHLPFPKDASLNKCSFLHPEPVVGSKMHKMPDLFIIGSGEAMLQLIPPFQRRHCQSVAMP
IEPGDIGYVDTTHWKVYVIARGVQPLVICDGTAFSEL

FIGURE 21

CCACGGTGTCCGTTCTTCGCCCCGGCGGCAGCTGTCCCCGAGGCGGGAGGAGCCCCGAGGGGCG
CGAGCCCCGCATGAATCATTGTAGTCAATCATTTTCCAGTTCTCAGCCGTTTCAGTTGTGATC
AAGGGACACGTGGTTTCCGAACTGCCAGCTCAGAATAGGAAAATAACTTGGGATTTTATATT
GGAAGACATGGATCTTGCTGCCAACGAGATCAGCATTTATGACAACTTTTCAGAGACTGTTG
ATTTGGTGAGACAGACCGGCCATCAGTGTGGCATGTCAGAGAAGGCAATTGAAAAATTTATC
AGACAGCTGCTGGAAAAGAATGAACCTCAGAGACCCCCCGCAGTATCCTCTCCTTATAGT
TGTGTATAAGGTTCTCGCAACCTTGGGATTAATCTTGCTCACTGCCTACTTTGTGATTCAAC
CTTTCAGCCCATTAGCACCTGAGCCAGTGCTTTGTGGAGCTCAC

FIGURE 22

CCCACGCGTCCGCCCACGCGTCCGGCTGAACACCTCTTCTTTGGAGTCAGCCACTGATGAGG
CAGGGTCCCCACTTGCAGCTGCAGCAGCTGCAGCAGCTGCAGAGCGCTGCTCCTGGCTGGTG
CCACTGGTGCACGCTGCTAGACCGTGCCTATGAGCCGCTGGGGCTGCAGTGGGGACTGCC
CTCCCTGCCACCCACCAATGGCAGCCCCACCTTCTTTGAAGACTTCCAGGCTTTTTGTGCCA
CACCCGAATGGCGCCACTTTCATCGACAAACAGGTACAGCCAACCATGTCCTCCAGTTCGAAATG
GACACGTATGCTAAGAGCCACGACCTTATGTGAGGTTTCTGGAATGCCTGCTATGACATGCT
TATGAGCAGTGGGCAGCGGCGCCAGTGGGAGCGCGCCAGAGTCGTGGGGCCTTCCAGGAGC
TGGTGCTGGAACCTGCGCAGAGGCGGGCGCGCTGGAGGGGCTACGCTACACGGCAGTGCTG
AAGCAGCAGGCAACGCAGCACTCCATGGCCCTGCTGCACTGGGGGGCGCTGTGGCGCCAGCT
CGCCAGCCCATGTGGGGCCTGGGCGCTGAGGGACACTCCCATCCCCGCTGGAAACTGTCCA
GCGCCGAGACATATTACGCATGCGTCTGAAGCTGGTGCCCAACCATCACTTCGACCCTCAC
CTGGAAGCCAGCGCTCTCCGAGACAATCTGGGTGAGGTTCCCTGACACCCACCGAGGAGGC
CTCACTGCCTCTGGCAGTGACCAAAGAGGCCAAAGTGAGCACCCACCCGAGTTGCTGCAGG
AGGACCAGCTCGGCGAGGACGAGCTGGCTGAGCTGGAGACCCGATGGAGGCAGCAGAACTG
GATGAGCAGCGTGAGAAGCTGGTGCTGTGGCCGAGTGCCAGCTGGTGACGGTAGTGGCCGT
GGTCCCAGGGCTGCTGGAGGTACCCACACAGAATGTATACTTCTACGATGGCAGCACTGAGC
GCGTGGAACCCGAGGAGGGCATCGGCTATGATTTCCGGCGCCCACTGGCCCACTGCGTGAG
GTCCACCTGCGGCGTTTCAACCTGCGCGTTTCAGCACTTGAGCTCTTCTTTATCGATCAGGC
CAACTACTTCCCTCAACTTCCCATGCAAGGTGGGCACGACCCCACTCTCATCTCCTAGCCAGA
CTCCGAGACCCAGCCTGGCCCCATCCCAACCCATACCCAGGTACGGAACCAAGGTGTACTCG
TGGCTCCTGCGCCTACGGCCCCCTCTCAAGGCTACCTAAGCAGCCGCTCCCCCAGGAGAT
GCTGCGTGCTCAGGCCTTACCCAGAAATGGGTACAGCGTGAGATATCCAACCTTCGAGTACT
TGATGCAACTCAACACCATTTGCGGGGCGGACCTACAATGACCTGTCTCAGTACCCGTGTGTT
CCCTGGGTCTGTCAGGACTACGTGTCCCAACCCCTGGACCTCAGCAACCCAGCCGTCTTCCG
GGACCTGTCTAAGCCCATCGGTGTGGTGAAACCCCAAGCATGCCAGCTCGTGAGGGAGAAGT
ATGAAAGCTTTGAGGACCCAGCAGGAGCCATGACCAAGTTCCACTATGGCACCCCACTACTCC
AATGCAGCAGGCGTGATGCACTACCTCATCCGCGTGGAGCCCTTCACCTCCCTGCACGTCCA
GCTGCAAGTGCGCGCTTTGACTGCTCCGACCGGCAGTTCCACTCGGTGGCGGCAGCCTGGC
AGGCACGCCTGGAGAGCCCTGCCGATGTGAAGGAGCTCATCCCGAATTCTTCTACTTTTCT
GACTTCCTGGAGAACCAGAACGGTTTTGACCTGGGCTGTCTCCAGCTGACCAACGAGAAGGT
AGGCGATGTGGTGCTACCCCGTGGGCCAGCTCTCCTGAGGACTTCATCCAGCAGCACCGCC
AGGCTCTGGAGTCGGAGTATGTGTCTGCACACCTACACGAGTGGATCGACCTCATCTTTGGC
TACAAGCAGCGGGGCCAGCCGCGGAGGACCCCTCAATGTCTTCTATTACTACCTACTGA
GGGGGCTGTAGACCTGGACCATGTGACAGATGAGCGGGAACGGAAGGCTCTGGAGGGCATT
TCAGCAACTTTGGGCAGACTCCCTGTGAGCTGCTGAAGGAGCCACATCCAACCTCGGCTCTCA
GCTGAGGAAGCAGCCCATCGCCTTGACGCCTGGACACTAACTCACCTAGCATCTTCCAGCA
CCTGGACGAACTCAAGGCATTCTTCGAGAGGTGACTGTGAGTGCCAGTGGGCTGCTGGGCA
CCCACAGCTGGTTGCCCTATGACCGCAACATAAGCAACTACTTCAGCTTCAGCAAAGACCCC
ACCATGGGCAGCCACAAGACGCAGCGACTGCTGAGTGGCCCGTGGGTGCCAGGCAGTGGTGT
GAGTGGACAAGCACTGGCAGTGGCCCCGGATGGAAAGCTGCTATTACGCGGTGGCCACTGGG
ATGGCAGCCTGCGGGTGACTGCACTACCCCGTGGCAAGCTGTTGAGCCAGCTCAGCTGCCAC
CTTGATGTAGTAACCTGCCTTGCACTGGACACCTGTGGCATCTACCTCATCTCAGGCTCCCG
GGACACCACGTGCATGGTGTTGGCGGCTCCTGCATCAGGGTGGTCTGTGAGTGGCCTGGCAC
CAAAGCCTGTGCAGGTCTGTATGGGCATGGGGCTGCAGTGAGCTGTGTGGCCATCAGCACT
GAACTTGACATGGCTGTGTCTGGATCTGAGGATGGAAGTGTGATCATACTGTACGCCG
CGGACAGTTTGTAGCGGCACTACGGCCTCTGGGTGCCACATTCCCTGGACCTATTTTCCACC
TGGCATTGGGGTCCGAAGGCCAGATTGTGGTACAGAGCTCAGCGTGGGAACGTCTGGGGCC
CAGGTACCTACTCCTTGACCTGTATTGAGTCAATGGGAAGTTGCGGGCTTCACTGCCCCCT
GGCAGAGCAGCCTACAGCCCTGACGGTGACAGAGGAACTTTGTGTTGCTGGGCAACCGCCAGT
GCGCCCTGCACATCCTCCAATAAACACACTGCTCCCGGCCGCGCCTCCCTTGCCCATGAAG
GTGGCCATCCGCAGCGTGGCCGTGACCAAGGAGCGCAGCCACGTGCTGGTGGGCCTGGAGGA
TGGCAAGCTCATCGTGGTGGTGGCGGGCAGCCCTCTGAGGTGCGCAGCAGCCAGTTTCGCGC
GGAAGCTGTGGCGGTCTCGCGGCGCATCTCCAGGTGTCTCGGGAGAGACGGAATACAAC
CCTACTGAGGCGCGCTGAAACCTGGCCAGTCCGGCTGCTCGGGCCCCGCCCCGGCAGGCCTG
GCCCCGGGAGGCCCCGCCAGAGTCCGGCGGGAACACCCCGGGGTGGGCAGCCAGGGGGTGA
GCGGGGGCCACCCTGCCAGCTCAGGGATTGGCGGGCGATGTTACCCCTCAGGGATTGGCG
GGCGGAAGTCCCGCCCCCTCGCCGGCTGAGGGGCCGCCCTGAGGGCCAGCACTGGCGTCT

FIGURE 23

MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLEGL
RYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLKLVPN
HHFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDELALETP
MEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFYDGSTERVETEEGIGYDFRRP
LAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTVPSSPSQTPRPQPGPIPPHTQV
RNQVYSWLLRLRPPSQGYLSSRSPQEMLRASGLTQKWVQREISNFEYLMQLNTIAGR TYNDL
SQYPVFPWVLQDYVSP TLDLSNPAVFRDLSKPIGVVNP KHAQLVREKYESFEDPAGTIDKFH
YGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFD CSDRQFHSVAAAWQARLESPADV KELIP
EFFYFPDFLENQNGFDLGCLQLTNEKVG DVVLPPWASSPEDFIQQRQA LESEYVSAHLHEW
IDLIFGYKQRGPAAEEALNVFYCTYEGAVDLDHVTDERERKALEGII SNFGQTPCQLLKEP
HPTRL SAE EAAHRLARLD TNSPSIFQHLDELKAFFAEVTVSASGLLGTHSWLPYDRNISNYF
SFSKDPTMGSHKTQRLLSGPWVPGSGVSGQALAVAPDGKLLFSGGHWDGSLRVTALPRGKLL
SQLSCHLDVV TCLALDTCGIY LISGRD TCMVWRLLHQGGLSVGLAPKPVQVLYGHGA AVS
CVAISTELDMAVSGSEDGTV I IHTVRRGQFVAALRPLGATFPGP I FHLALGSEGQIVVQSSA
WERPGAQVTYSLHLYSVNGKL RASLPLAEQPTALT VTEDFVLLGTAQCALHILQLNTLLPAA
PPLPMKVAIRSVAVTKERSHVLVGLEDGKLIVVAGQPSEVRSSQFARKLWRSSRRISQVSS
GETEYNPTEAR

FIGURE 24

CGGACGCGTGGGCGGACGCGTGGGGGCTGTGAGAAAGTGCCAATAAATACATCATGCAACCC
CACGGCCACCTTGTGAACTCCTCGTGCCAGGGCTGATGTGCGTCTTCCAGGGCTACTCAT
CCAAAGGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCCTGGGGCTCTTC
TGGACCCTTAACTGGGTACTGGCCCTGGGCCAATGCGTCCTCGCTGGAGCCTTTGCCTCCTT
CTACTGGGCCTTCCACAAGCCCCAGGACATCCCTACCTTCCCCTTAATCTCTGCCTTCATCC
GCACACTCCGTTACCACACTGGGTCAATTGGCATTGAGGCCCTCATCCTGACCCTTGTGCAG
ATAGCCCGGGTCATCTTGGAGTATATTGACCACAAGCTCAGAGGAGTGCAGAACCTGTAGC
CCGCTGCATCATGTGCTGTTTCAAGTGCTGCCTCTGGTGTCTGGAAAAATTTATCAAGTTCC
TAAACCGCAATGCATACATCATGATCGCCATCTACGGGAAGAATTTCTGTGTCTCAGCCAAA
AATGCGTTCATGCTACTCATGCGAAACATTGTGAGGGTGGTCGTCCTGGACAAAGTCACAGA
CCTGCTGCTGTTCTTTGGGAAGCTGCTGGTGGTCGGAGGCGTGGGGGTCTGTCTTCTTTT
TTTTCTCCGGTCGCATCCCGGGGCTGGGTAAAGACTTTAAGAGCCCCACCTCAACTATTAC
TGGCTGCCCATCATGACCTCCATCCTGGGGGCTATGTCATCGCCAGCGGCTTCTTCAGCGT
TTTCGGCATGTGTGTGGACACGCTCTTCTCTGCTTCTTGAAGACCTGGAGCGGAACAACG
GCTCCCTGGACCGGCCCTACTACATGTCCAAGAGCCTTCTAAAGATTCTGGGCAAGAAGAAC
GAGGCGCCCCCGGACAACAAGAAGAGGAAGAAGTGAAGCTCCGGCCCTGATCCAGGACTGC
ACCCACCCCCACCGTCCAGCCATCCAACCTCACTTCGCCTTACAGGTCTCCATTTTGTGGT
AAAAAAGGTTTTAGGCCAGGCGCCGTGGCTCACGCCTGTAATCCAACACTTTGAGAGGCTG
AGGCGGGCGGATCACCTGAGTCAGGAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTCC
GTCTCTATTAAAAATACAAAAATTAGCCGAGAGTGGTGGCATGCACCTGTCATCCCAGCTAC
TCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCGAGA
TCGCGCCACTGCACTCCAACCTGGGTGACAGACTCTGTCTCCAAAACAAAACAAACAA
AAAGATTTTATTAAAGATATTTTGTTAACCTC

FIGURE 25

RTRGRTRGGCEKVPINTSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLGLF
WTLNWWLALGQCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGALILTLVQ
IARVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNFCVSAK
NAFMLLMRNIVRVVLDKVTDLLLFFGKLLVVGGVGLSFFFFSGRIPGLGKDFKSPHLNYY
WLPIMTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSLDRPYMSKSLKILGKKN
EAPPDNKKRKK

FIGURE 26

GAGTCTTGACCGCCGCCGGGCTCTTGGTACCTCAGCGCGAGCGCCAGGCGTCCGGCCGCCGT
GGCTATGTTTCGTGTCCGATTTCCGCAAAGAGTTCTACGAGGTGGTCCAGAGCCAGAGGGTCC
TTCTCTTCGTGGCCTCGGACGTGGATGCTCTGTGTGCGTGCAAGATCCTTCAGGCCTTGTTT
CAGTGTGACCACGTGCAATATACGCTGGTTCAGTTTCTGGGTGGCAAGAACTTGAACTGC
ATTTCTTGAGCATAAAGAACAGTTTTCATTATTTTATTCTCATAACTGTGGAGCTAATGTAG
ACCTATTGGATATTCTTCAACCTGATGAAGACACTATATTCTTTGTGTGTGACTCCCATAGG
CCAGTCAATGTCGTCAATGTATACAACGATACCCAGATCAAATTACTCATTAAACAAGATGA
TGACCTTGAAGTTCCCGCCTATGAAGACATCTTCAGGGATGAAGAGGAGGATGAAGAGCATT
CAGGAAATGACAGTGATGGGTGAGAGCCTTCTGAGAAGCGCACACGGTTAGAAGAGGAGATA
GTGGAGCAAACCATGCGGAGGAGGCAGCGGCGAGAGTGGGAGGCCCGGAGAAGAGACATCCT
CTTTGACTACGAGCAGTATGAATATCATGGGACATCGTCAGCCATGGTGATGTTTGAGCTGG
CTTGGATGCTGTCCAAGGACCTGAATGACATGCTGTGGTGGGCCATCGTTGGACTAACAGAC
CAGTGGGTGCAAGACAAGATCACTCAAATGAAATACGTGACTGATGTTGGTGTCTGCAGCG
CCACGTTTCCCGCCACAACCACCGGAACGAGGATGAGGAGAACACACTCTCCGTGGACTGCA
CACGGATCTCCTTTGAGTATGACCTCCGCCTGGTGCTCTACCAGCACTGGTCCCTCCATGAC
AGCCTGTGCAACACCAGCTATACCGCAGCCAGGTTCAAGCTGTGGTCTGTGCATGGACAGAA
GCGGCTCCAGGAGTTCCTTGACAGCATGGGTCTTCCCCTGAAGCAGGTGAAGCAGAAGTTCC
AGGCCATGGACATCTCCTTGAAGGAGAATTTGCGGGAAATGATTGAAGAGTCTGCAAATAAA
TTTGGGATGAAGGACATGCGCGTGACAGCTTTCAGCATTCATTTTGGGTTCAAGCACAAGTT
TCTGGCCAGCGACGTGGTCTTTGCCACCATGTCTTTGATGGAGAGCCCCGAGAAGGATGGCT
CAGGGACAGATCACTTCATCCAGGCTCTGGACAGCCTCTCCAGGAGTAACCTGGACAAGCTG
TACCATGGCCTGGAACCTGCCAAGAAGCAGCTGCGAGCCACCCAGCAGACCATTGCCAGCTGC
CTTTGCACCAACCTCGTCATCTCCCAGGGGCCTTTCCTGTACTGCTCTCTCATGGAGGGCAC
TCCAGATGTCATGCTGTTCTCTAGGCCGGCATCCCTAAGCCTGCTCAGCAAACACCTGCTCA
AGTCCCTTTGTGTGTTTCGACAAAGAACCGGCGCTGCAAACCTGCTGCCCCCTGGTGATGGCTGCC
CCCCCTGAGCATGGAGCATGGCACAGTGACCGTGGTGGGCATCCCCCAGAGACCGACAGCTC
GGACAGGAAGAACTTTTTTGGGAGGGCGTTTGAGAAGGCAGCGGAAAGCACCAGCTCCCGGA
TGCTGCACAACCATTTTTGACCTCTCAGTAATTGAGCTGAAAGCTGAGGATCGGAGCAAGTTT
CTGGACGCACTTATTTCCCTCCTGTCTAGGAAATTGATTCTTCCAGAATGACCTTCTTATT
TATGTAACCTGGCTTTTCAATTAGATTGTAAGTTATGGACATGATTTGAGATGTAGAAGCCATT
TTTTATTAAATAAAATGCTTATTTTAGGAAA

FIGURE 27

MFVSDFRKEFYEVVQSQRVLLFVASDVDALCACKILQALFQCDHVQYTLVPVSGWQELETAF
LEHKEQFHYFILINCGANVDLLDILQPDEDTIFFVCDSHRPVNVVNVYNDTQIKLLIKQDDD
LEVPAIEDIFRDEEEDEEHSGNDSGSEPSEKTRLEEEIVEQTMRRRQRREWEARRRDILF
DYEQYEHGTSSAMVMFELAWMLSKDLNDMLWWAIVGLTDQWVQDKITQMKYVTDVGVLRH
VSRHNRNEDEENTLSVDCTRISFEYDLRLVLYQHWSLHDSL CNTSYTAARFKLWSVHGQKR
LQEF LADMGLPLKQVKQKFQAMD ISLKENLREMI EESANKFGMKDMRVQTFSIHFGFKHKFL
ASDVVFATMSLMESPEKDGSGTDHFIQALDSLRSNLDKLYHGLELAKKQLRATQQTIASCL
CTNLVISQGPFLYCSLMEGTPDVMLFSRPASLSLLSKHLLKSFVCSTKNRRCKLLPLVMAAP
LSMEHGTVTTVVGIPPETDSSDRKNFFGRAFEKAAESTSSRMLHNHFDLSVIELKAEDRSKFL
DALISLLS

FIGURE 28

GTACCTCAGCGCGAGCGCCAGGCGTCCGGCCGCGCGTGGCTATGNTCGTGTCCGATTTCCGCA
AAGAGTTCTACGAGGTGGTCCAGAGCCAGAGGGTCCTTCTCTTCGTGGCCTCGGANGTGGAT
GCTCTGTGTGCGTGCAAGATCCTTCAGGCCTTGTTCCAGTGTGACCANGTGCAATATANGCT
GGTTCAGTTTCTGGGTGGCAAGAAGCTTGAAACTGCATTTCTTGAGCATAAAGAACAGTTTC
ATTATTTTATTCTCATAAACTGTGGAGCTAATGTAGACCTATTGGATATTCTTCAACCTGAT
GAAGACACTATATTCTTTGTGTGTGACACCCATAGGCCAGTCAATGTTGTCAATGTATACAA
CGATACCC

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FIGURE 29

CAGGAACCCTCTCTTTGGGTCTGGATTGGGACCCCTTTCCAGTACCATTTTTTCTAGTGAAC
CACGAAGGGACGATACCAGAAAACACCCTCAACCCAAAGGAAATAGACTACAGCCCCAATTG
GCTGACTTTTGGCTATAGAAAAAGAAAGGAACGAAAAGAGACAGTTTTTTTTTGGAAAGCTAA
GTCTTCCCTTTATCGAGTCAAGAAACCCCCCTTCTTGAGCTATTTACAGCTTTTAACAATT
GAGTAAAGTACGCTCCGGTCACCATGGTGACAGCCGCCCTGGGTCCCGTCTGGGCAGCGCTC
CTGCTCTTTCTCCTGATGTGTGAGATCCGTATGGTGGAGCTCACCTTTGACAGAGCTGTGGC
CAGCGGCTGCCAACGGTGCTGTGACTCTGAGGACCCCTGGATCCTGCCCATGTATCCTCAG
CCTCTTCTCCTCCGGCCGCCCCACGCCCTGCCCTGAGATCAGACCCTACATTAATATCACCATC
CTGAAGGGTGACAAAGGGGACCCAGGCCCAATGGGCCTGCCAGGGTACATGGGCAGGGAGGG
TCCCCAAGGGGAGCCTGGCCCTCAGGGCAGCAAGGGTGACAAGGGGGAGATGGGCAGCCCCG
GCGCCCCGTGCCAGAAGCGCTTCTTCGCCTTCTCAGTGGGCCGCAAGACGGCCCTGCACAGC
GGCGAGGACTTCCAGACGCTGCTCTTCGAAAGGGTCTTTGTGAACCTTGATGGGTGCTTTGA
CATGGCGACCGGCCAGTTTGCTGCTCCCTGCGTGGCATCTACTTCTTCAGCCTCAATGTGC
ACAGCTGGAATTACAAGGAGACGTACGTGCACATTATGCATAACCAGAAAGAGGCTGTCTATC
CTGTACGCGCAGCCCAGCGAGCGCAGCATCATGCAGAGCCAGAGTGTGATGCTGGACCTGGC
CTACGGGGACCGCGTCTGGGTGCGGCTCTTCAAGCGCCAGCGCGAGAACGCCATCTACAGCA
ACGACTTCGACACCTACATCACCTTCAGCGGCCACCTCATCAAGGCCGAGGACGAGTGAGG
CCTCTGGGCCACCCCTCCCGCTGGAGAGCTCAGGTGCTGGTCCCGTCCCTGCAGGGCTCAG
TTTGCACTGCTGTGAAGCAGGAAGGCCAGGGAGGTCCCCGGGGACCTGGCATTTCTGGGGAGA
CCCTGCTTCTATCTTGGCTGCCATCATCCCTCCCAGCCTATTTCTGCTCCTCTCTTCTCTCT
TGGACCTATTTTAAGAAGCTTGCTAACCTAAATATTCTAGAACTTTCCCAGCCTCGTAGCCC
AGCACTTCTCAAACCTTGGAATGCATGCGAATCACCCGGGGTTTCGTGTTAAATGCAGATTCT
GACTCAGCAGGTCTGAGTGGGTCCAGGATTCTGTGTTTTCTCATATGTTCTTGGGTGATGCTG
ATGGGGTCAGTCTATGAACCACACTGGAGCAACCAGGTTCTAGGACTTTCTCAATATTCTAG
TACTTTCTGAACATTCTGGAATCCTCCCCACATTCTAGAATTCTCCCAACATTTTTTTTTCT
TGAGACAGAGTCTTGCTCTGTTGCCAGGCTAGAGTGCAGTGGTGCAATCTCAGTTCACCTGC
AACCTCTGCCTCCCGGGTTCAAGCGATTCTTCTGCCTCAGCCTCCCTAGTGGCTGGGATTAC
AGGCGCCTGCTACCATGCCTGGCTAATTTTTGTATTTTTAGTAGAGATGGGGTTTCACCATA
TTGGCCAGGCTGGTCTTGAACCTCCTGACTTCAGGTGACCCACCCGCTCGGCCTCTCAAAT
GCTGGGATTACAGGTGTGAGCCACCGTGCCTGGCCAATTCCAACATTCTTAAATTCTCTCAT
CCCTCCAGGGCTCCCGTGTATGTTCTCTTTACCCCTTCCCCCTCTTCTCTTGCTCAGGCC
TGCACCACTGCAGCCACCGTTCAATTTATTCAATTATAAACACTGAGCACTCACTCTGTGCT
GGGTCCCGGGAGGGTGAGGGGTGAGGAGCTCAGACAGGCCCTGCCCTGCCCTCAGTGACTGGCCA
GTCCAGCCCAGGCGGGGAGAGATGTGTACATAGGTTTTTAAAGCAGACCCAGAGCTCATGGGG
GCCTGTGTTCTGGGTGTTTCAAGTGCTGCTGGTCCCTCCATTACCCACTGCTCCCCAAGGCTGG
TGGGACGGGGTCCCGGTGGCAGGGGCAGGTATCTCCTTCCCGTTCTCATCCACCTGCCAG
TGCTCATCGTTACAGCAAACCCAGGGGGCTTGGCCAGGTCAAGGGTTCTGTGAGGAGAGG
ACCCAGGAGTGTGGGGGCATTTGGGGGGTGAAGTGGCCCCCGAAGAATGGAACCCACACCCA
TAGCTCTCCCCACAGCTGATACGGCATCCTGCGAGAAGACCTGCCCTCCTCACTGGGATCCC
CTTCTGCTCCTCCTCCAGGGCTCTGCCAGGGCCTTGCTCAGTCCCTTCCACCAAGTCACT
GAACCTCCGTTTTCCCCAGGGCCTCCAGTGCCTCAGACACTGATGTCTGTCCCCAGGTGCT
CTCTGCCCCCTCATGCCCCCTCTCACCGGCCAGTGCCCCGACTCTCCAGGCTTTATCAAGGTG
CTAAGGCCCGGGTGGGCAGCTCCTCGTCTCAGAGCCCTCCTCCGGCCTGGTGTGCTTCTTAC
AAACACCTGCAGGAGAAGGGCCACGGAAGCCCCAGGCTTTAGAGCCCTCAGCAGGTCTGGGG
AGCTAGAGCAAAGGAGGGACCTCAGGCCTTCCGTTTCTTCTTCCAGGGTGGGGTGGCCTGGT
GTTCCCTTAGCCTTCCAAACCCAGGTGGCCTGCCCTTCTCCCCAGAGGGAGGCGGCCTCCGC
CCATTGGTGCTCATGCAGACTCTGGGGCTGAGGTGCCCGGGGGGTGATCTCTGGTGCTCAC
AGCCGAGGGAGCCGTGGCTCCATGGCCAGATGACGGAACAGGGTCTGACCAAGTGCCAGGA
AGACCTGTGTATATAAACACCCTGCCTGATCCTGCCCTGCCTGACCCGCCACGCCCTGCC
GTCCAGCATGATTAAAGAATGCTGTCTCTTGGAAAAA

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FIGURE 30

MVTAALGPVWAALLLFLLMCEIRMVELTFDRAVASGCQRCCDSEDPLDPAHVSSASSSSGRPH
ALPEIRPYINITILKGDKGDPGPMGLPGYMGREGPQGEPPQGSKGDKGEMGSPGAPCQKRF
FAFSVGRKTALHSGEDFQTLLFERVFNLDGCFDMATGQFAAPLRGIYFFSLNVHSWNYKET
YVHIMHNQKEAVILYAQPSESRIMQSQSVMLDLAYGDRVWVRLFKRQRENAIYSNDFDTYIT
FSGHLIKAEDD

Important features:

Signal peptide:

amino acids 1-20

N-glycosylation site.

amino acids 72-75

Clq domain proteins.

amino acids 144-178, 78-111 and 84-117

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FIGURE 31

ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCCTCGGGCCCGACCCGCCAGGAAAGACTG
AGGCCGCGGGCTGCCCCGCCCCGGCTCCCTGCGCCGCGCCGCTCCCGGGACAGAAGATGTG
CTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGGTGCAGG
GCTGCCCATCCGGCTGCCAGTGCAGCCAGCCACAGACAGTCTTCTGCACTGCCCCGCCAGGGG
ACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTGAGAACGGCAT
CACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGCCTGCAGCTCCTGGACCTGTAC
AGAACCAGATCGCCAGCCTGCCAGCGGGGTCTTCCAGCCACTCGCCAACCTCAGCAACCTG
GACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCCGTGGCCTGCGGCGCCT
CGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGCCTGGTGCCTTCGACACGC
TCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGCGGGCACTGCCCCGCTGCGC
CTGCCCCGCTGCTGCTGCTGGACCTCAGCCACAACAGCCTCCTGGCCCTGGAGCCCGGCAT
CCTGGACACTGCCAACGTGGAGGCGCTGCGGCTGGCTGGTCTGGGGCTGCAGCAGCTGGACG
AGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACCTGGATGTGTCCGACAACAGCTGGAG
CGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCCTGACGCGCCTGCGGCTGGCCGGCAACAC
CCGCATTGCCCAGCTGCGGCCCGAGGACCTGGCCGGCCTGGCTGCCCTGCAGGAGCTGGATG
TGAGCAACCTAAGCCTGCAGGCCCTGCCTGGCGACCTCTCGGGCCTCTTCCCCCGCCTGCGG
CTGCTGGCAGCTGCCCGCAACCCCTTCAACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCTG
GGTGCGCGAGAGCCACGTCAACTGGCCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCA
AGAACGCTGGCCGGCTGCTCCTGGAGCTTGACTACGCCGACTTTGGCTGCCAGCCACCACC
ACCACAGCCACAGTGCCCAACCACGAGGCCCCGTGGTGCGGGAGCCACAGCCTTGTCTTCTAG
CTTGGCTCCTACCTGGCTTAGCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCA
CTGCCCCACCGACTGTAGGGCCTGTCCCCCAGCCCCAGGACTGCCACCGTCCACCTGCCTC
AATGGGGGCACATGCCACCTGGGGACACGGCACCACTGGCGTGCTTGTGCCCCGAAGGCTT
CACGGGCCTGTACTGTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCA
CGCCGAGGCCACCACGGTCCCTGACCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGC
GTGGGGCTGCAGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTA
TCGCAACCTATCGGGCCCTGATAAGCGGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTG
AGTACACGGTCACCCAGCTGCGGCCCAACGCCACTTACTCCGTCTGTGTATGCCTTTGGGG
CCCCGGGCGGGTGCCGGAGGGCGAGGAGGCCTGCGGGGAGGGCCATAACCCCCAGCCGTCCA
CTCCAACCACGCCCCAGTCACCCAGGCCCGCGAGGGCAACCTGCCGCTCCTCATTGCGCCCCG
CCCTGGCCGCGGTGCTCCTGGCCGCGCTGGCTGCGGTGGGGGACGCTACTGTGTGCGGCGG
GGGCGGGCCATGGCAGCAGCGGCTCAGGACAAAGGGCAGGTGGGGCCAGGGGCTGGGCCCT
GGAAGTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCAGGCAACAGAGGGCGGTGGAG
AGGCCCTGCCAGCGGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCAGGGCCTGGCCTC
CAGTCACCCCTCCACGCAAAGCCCTACATCTAAGCCAGAGAGAGACAGGGCAGCTGGGGCCG
GGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTGCTGCCACACCACGTAAGTTCTCAGTCC
CAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGACCACAGCTGGGCCCTGTTCCCTCTGGA
CCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCCCTAACGTCCCCAGAAC
CGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTGCAGTCCCTGGGCACGGCG
GGCCCTGCCATGTGCTGGTAACGCATGCCTGGGTCCCTGCTGGGCTCTCCCACTCCAGGCGGA
CCCTGGGGGCCAGTGAAGGAAGCTCCCGAAAGAGCAGAGGGAGAGCGGGTAGGCGGCTGTG
TGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAAGAACTGGAAAGGAAGATGCTTTA
GGAACATGTTTTGCTTTTTTAAATATATATATTTATAAGAGATCCTTTCCCATTTATTCTG
GGAAGATGTTTTTCAAACCTCAGAGACAAGGACTTTGGTTTTTTGTAAGACAAACGATGATATG
AAGGCCTTTTGTAAGAAAAAATAAAAGATGAAGTGTGAAA

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FIGURE 32

MCSRVP L L L L L L L L L L A L G P G V Q G C P S G C Q C S Q P Q T V F C T A R Q G T T V P R D V P P D T V G L Y V F E N
G I T M L D A G S F A G L P G L Q L L D L S Q N Q I A S L P S G V F Q P L A N L S N L D L T A N R L H E I T N E T F R G L R
R L E R L Y L G K N R I R H I Q P G A F D T L D R L L E L K L Q D N E L R A L P P L R L P R L L L L D L S H N S L L A L E P
G I L D T A N V E A L R L A G L G L Q Q L D E G L F S R L R N L H D L D V S D N Q L E R V P P V I R G L R G L T R L R L A G
N T R I A Q L R P E D L A G L A A L Q E L D V S N L S L Q A L P G D L S G L F P R L R L L A A A R N P F N C V C P L S W F G
P W V R E S H V T L A S P E E T R C H F P P K N A G R L L L E L D Y A D F G C P A T T T T A T V P T T R P V V R E P T A L S
S S L A P T W L S P T A P A T E A P S P P S T A P P T V G P V P Q P Q D C P P S T C L N G G T C H L G T R H H L A C L C P E
G F T G L Y C E S Q M G Q G T R P S P T P V T P R P P R S L T L G I E P V S P T S L R V G L Q R Y L Q G S S V Q L R S L R L
T Y R N L S G P D K R L V T L R L P A S L A E Y T V T Q L R P N A T Y S V C V M P L G P G R V P E G E E A C G E A H T P P A
V H S N H A P V T Q A R E G N L P L L I A P A L A A V L L A A L A A V G A A Y C V R R G R A M A A A A Q D K G Q V G P G A G
P L E L E G V K V P L E P G P K A T E G G G E A L P S G S E C E V P L M G F P G P G L Q S P L H A K P Y I

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FIGURE 33

GAATCATCCACGCACCTGCAGCTCTGCTGAGAGAGTGAAGCCGTGGGGGTTTTGAGCTCAT
CTTCATCATTCATATGAGGAAATAAGTGGTAAATCCTTGGAATACAATGAGACTCATCAG
AAACATTTACATATTTTGTAGTATTGTTATGACAGCAGAGGGTGATGCTCCAGAGCTGCCAG
AAGAAAGGGAAGTATGACCAACTGCTCCAACATGTCTCTAAGAAAGGTTCCCGCAGACTTG
ACCCAGCCACAACGACACTGGATTTATCCTATAACCTCCTTTTTCAACTCCAGAGTTCAGA
TTTTATTCTGTCTCCAACTGAGAGTTTTGATTCTATGCCATAACAGAATTCACAGCTGG
ATCTCAAAACCTTTGAATTCACAAGGAGTTAAGATATTTAGATTTGTCTAATAACAGACTG
AAGAGTGTAACTTGGTATTTACTGGCAGGTCTCAGGTATTTAGATCTTTCTTTAATGACTT
TGACACCATGCCATCTGTGAGGAAGCTGGCAACATGTCACACCTGGAAATCCTAGGTTTGA
GTGGGGCAAAAATACAAAATCAGATTTCCAGAAAATTGCTCATCTGCATCTAAATACTGTC
TTCTTAGGATTCAGAACTCTTCTCATTATGAAGAAGGTAGCCTGCCCATCTTAAACACAAC
AAAAGTGCACATTGTTTTACCAATGGACACAAATTTCTGGGTTCTTTGCGTGATGGAATCA
AGACTTCAAAAATATTAGAAATGACAAATATAGATGGCAAAAGCCAATTTGTAAGTTATGAA
ATGCAACGAAATCTTAGTTTAGAAAATGCTAAGACATCGGTTCTATTGCTTAATAAAGTTGA
TTTACTCTGGGACGACCTTTTCTTATCTTACAATTTGTTTGGCATAACATCAGTGGAACT
TTCAGATCCGAAATGTGACTTTTGGTGGTAAGGCTTATCTTGACCACAATTCATTTGACTAC
TCAAATACTGTAATGAGAACTATAAAATGGAGCATGTACATTTAGAGTGTTTTACATTC
ACAGGATAAAAATCTATTTGCTTTTGACCAAAATGGACATAGAAAACCTGACAATCTCAAATG
CACAAATGCCACACATGCTTTTCCCGAATTATCTACGAAATTCATATTTTAAATTTTGGC
AATAATATCTTAACAGACGAGTTGTTTAAAAGAACTATCCAAGTGCCTCACTTGAAAACCT
CATTTTGAATGGCAATAAACTGGAGACACTTTCTTTAGTAAGTTGCTTTGCTAACAACACAC
CCTTGGAACACTTGATCTGAGTCAAAATCTATTACAACATAAAAATGATGAAAATTGCTCA
TGGCCAGAACTGTGGTCAATATGAATCTGTCATACAATAAATTGCTGATTCTGTCTTCAG
GTGCTTGCCCAAAAGTATTCAAATACTTGACCTAAATAATAACCAATCCAACTGTACCTA
AAGAGACTATTCTGATGGCCTTACGAGAACTAAATATTGCATTTAATTTCTAACTGAT
CTCCCTGGATGCAGTCATTTAGTAGACTTTTCTGAGTCTGAACATTGAAATGAATCTTCT
CAGCCCATCTCTGGATTTTGTTCAGAGCTGCCAGGAAGTTAAAACCTCTAAATGCGGGAAGAA
ATCCATTCCGGTGTACCTGTGAATTAATAAATTTTCTTCTGAAACATATTCAGAGGTC
ATGATGGTTGGATGGTCAGATTCATACACCTGTGAATACCCTTTAAACCTAAGGGGAAGT
GTTAAAAGACGTTCTCTCCACGAATTATCTTGCAACACAGCTCTGTTGATTGTCACCATTG
TGGTTATTATGCTAGTTCTGGGGTTGGCTGTGGCCTTCTGCTGTCTCCACTTTGATCTGCCC
TGGTATCTCAGGATGCTAGGTCAATGCACACAACATGGCACAGGGTTAGGAAAACAACCCA
AGAACAACCTCAAGAGAAATGTCCGATTCCACGCATTTATTTTATACAGTGAACATTCATCTC
TGTGGGTGAAGAATGAATTGATCCCCAATCTAGAGAAGGAAGATGGTTCTATCTTGATTTGC
CTTTATGAAAGCTACTTTGACCCTGGCAAAAGCATTAGTGAATAATTGTAAGCTTCATTGA
GAAAAGCTATAAGTCCATCTTTGTTTTGTCTCCCAACTTTGTCCAGAATGAGTGGTGGCATT
ATGAATTCTACTTTGCCCACCACAATCTCTTCCATGAAAATTCTGATCATATAATTCTTATC
TTACTGGAACCCATTCCATTCTATTGCATTCCCACCAGGTATCATAACTGAAAAGCTCTCCT
GGAAAAAAGCATACTTGGAATGGCCCAAGGATAGGCGTAAATGTGGGCTTTTCTGGGCAA
ACCTTCGAGCTGCTATTAATGTTAATGTATTAGCCACCAGAGAAATGTATGAACTGCAGACA
TTCACAGAGTTAAATGAAGAGTCTCGAGGTTCTACAATCTCTCTGATGAGAACAGATTGTCT
ATAAAATCCCACAGTCCTTGGGAAGTTGGGGACCACATACACTGTTGGGATGTACATTGATA
CAACCTTTATGATGGCAATTTGACAATATTTATTAATAAATAAATAAGTTATTCCCTTCATA
TCAGTTTCTAGAAGGATTTCTAAGAATGTATCCTATAGAAACACCTTCACAAGTTTATAAGG
GCTTATGAAAAAGGTGTTTCATCCCAGGATTGTTTATAATCATGAAAATGTGGCCAGGTGC
AGTGGCTCACTCTTGTAATCCCAGCACTATGGGAGGCCAAGGTGGGTGACCCACGAGGTCAA
GAGATGGAGACCATCCTGGCCAACATGGTGAAACCCTGTCTCTACTAAAAATACAAAATTA
GCTGGGCGTGATGGTGCACGCCTGTAGTCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATCG
CTTGAACCCGGGAGGTGGCAGTTGCAGTGAGCTGAGATCGAGCCACTGCACTCCAGCCTGGT
GACAGAGCGAGACTCCATCTCAAAAAAAGAAAAAAGAAAAAAGAAAAAATGGAAAAACATCC
TCATGGCCACAAAATAAGGTCTAATTCAATAAATTATAGTACATTAATGTAATATAATATTA
CATGCCACTAAAAAGAATAAGGTAGCTGTATATTTCTGGTATGGAAAAACATATTAATAT
GTTATAAACTATTAGGTTGGTGCAAACTAATTGTGGTTTTTGGCATTGAAATGGCATTGAA
ATAAAAGTGTAAGAAATCTATACCAGATGTAGTAACAGTGGTTTTGGTCTGGGAGGTTGGA
TTACAGGGAGCATTTGATTTCTATGTTGTGTATTTCTATAATGTTTGAATTGTTTAGAATGA
ATCTGTATTTCTTTTATAAGTAGAAAAAATAAAGATAGTTTTTACAGCCT

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FIGURE 34

MRLIRNIYIFCSIVMTAEGDAPELPEERELMTNCSNMSLRKVPADLTPATTTLDLSYNLLFQ
LQSSDFHSVSKLRVLILCHNRIQQDLKTFEFNKELRYLDLSNNRLKSVTWYLLAGLRYLDL
SFNDFDTMPICEEAGNMSHLEILGLSGAKIQKSDFQKIAHLHLNTVFLGFRTLPHYEEGSLP
ILNTTKLHIVLPMDTNFWVLLRDGIKTSKILEMTNIDGKSQFVSYEMQRNLSLENAKTSVLL
LNKVDLLWDDLFLILQFVWHTSVEHFQIRNVTFGGKAYLDHNSFDYSNTVMRTIKLEHVHFR
VFYIQQDKIYLLLTkMDIENLTISNAQMPHMLFPNYPTKFQYLNfANNILTDELfKRTIQLP
HLKTLILNGNKLETLSLVSCFANNTPLEHLDLSQNLQHKNDENCsWPETVVNMNLSYNKLS
DSVFRCLPKSIQILDNNNIQTVPKETIHLMALRELNIAFNFLTDLPGCSHfSRLSVLNIE
MNFILSPSLDFVQSCQEVKTLNAGRNPFRCTCELKNFIQLETYSEVMMVGWSDSYTCEYPLN
LRGTRLKDVHLHELSCNTALLIVTIVVIMLVGLAVAFCLHFDLPWYLRMLGQCTQTWHRV
RKTTQEQLKRNVRFHAFISYSEHDSLWVKNELIPNLEKEDGSILICLYESYfDPGKSISENI
VSFIEKSYKSIFVLSPNFVQNEWCHYEFYFAHhNLFHENSdHIILILLEPIPFYCIPTRYHK
LKALLEKKAYLEWPKDRRCGLFWANLRAAINVNVLATREMYELQTFTELNEESRGSTISLM
RTDCL

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FIGURE 35A

GGGGGCTTTCTTGGGCTTGGCTGCTTGGAAACACCTGCCTCCAAGGACCGGCCTCGGAGGGGT
CGCCGGGAAAGGGAGGGAAGAAGGAAGGGCGGGGCCGGCCCCCTGCGCCCGCCCCGCGCCT
CTGCGCGCCCCCTGTCCGCCCCGGCCCCAGCCCAGCCCAGCCCCGCGGGCCGGTCAACGCGCA
GCCAGCCGGCCGCTCCCGCGCCCAAGCGCGCCGCTCTGCTGTGCCCTGCGCCCTTGCCCCG
CGCCAGCTTCTGCGCCCGCAGCCCCGCCCGCGCCCCCGGTGACCGTGACCCTGCCCTGGGCG
CGGGGCGGAGCAGGCATGCTCCCGCCCCGGGACCGCTACCCAGCGCTGGCCCTGGTGCTCT
GGCAGTGACCCTGGCCGGGGTCGGAGCCCAGGGCGCAGCCCTCGAGGACCCTGATTATTACG
GGCAGGAGATCTGGAGCCGGGAGCCCTACTACGCGCGCCCGAGCCCGAGCTCGAGACCTTC
TCTCCGCCGCTGCCTGCGGGGCCCGGGGAGGAGTGGGAGCGGCGCCCGCAGGAGCCCAGGCC
GCCCAAGAGGGCCACCAAGCCCAAGAAAGCTCCCAAGAGGGAGAAGTCGGCTCCGGAGCCGC
CTCCACCAGGTAAACACAGCAACAAAAAGTTATGAGAACCAAGAGCTCTGAGAAGGCTGCC
AACGATGATCACAGTGTCCGTGTGGCCCGTGAAGATGTCAGAGAGAGTTGCCACCTCTTGG
TCTGGAACCTTAAAAATCACAGACTTCCAGCTCCATGCCTCCACGGTGAAGCGCTATGGCC
TGGGGGCACATCGAGGGAGACTCAACATCCAGGCGGGCATTAATGAAAATGATTTTTATGAC
GGAGCGTGGTGCGCGGGAAGAAATGACCTCCAGCAGTGGATTGAAGTGGATGCTCGGCGCCT
GACCAGATTCATGGTGTCACTCACTCAAGGGAGGAACTCCCTCTGGCTGAGTGAAGTGGTGA
CATCCTATAAGGTCATGGTGAGCAATGACAGCCACACGTGGGTCACTGTTAAGAATGGATCT
GGAGACATGATATTTGAGGGAACAGTGAGAAGGAGATCCCTGTTCTCAATGAGCTACCCGT
CCCCATGGTGGCCCGCTACATCCGCATAAACCCCTCAGTCCTGGTTTGATAATGGGAGCATCT
GCATGAGAATGGAGATCCTGGGCTGCCACTGCCAGATCCTAATAATTATTATCACCGCCGG
AACGAGATGACCACCACTGATGACCTGGATTTAAGCACCACAATTATAAGGAAATGCGCCA
GTTGATGAAAGTTGTGAATGAAATGTGTCCCAATATCACAGAAATTTACAACATTGGAAAAA
GCCACCAGGGCCTGAAGCTGTATGCTGTGGAGATCTCAGATCACCTGGGGAGCATGAAGTC
GGTGAGCCCGAGTTCCACTACATCGCGGGGGCCACGGCAATGAGGTGCTGGGCCGGGAGCT
GCTGCTGCTGCTGGTGCAGTTCGTGTGTGAGGAGTACTTGGCCCGGAATGCGCGCATCGTCC
ACCTGGTGGAGGAGACGCGGATTCACGTCTTCCCTCCCTCAACCCCGATGGCTACGAGAAG
GCCTACGAAGGGGGCTCGGAGCTGGGAGGCTGGTCCCTGGGACGCTGGACCCACGATGGAAT
TGACATCAACAACAACCTTTCCTGATTTAAACACGCTGCTCTGGGAGGCAGAGGATCGACAGA
ATGTCCCCAGGAAAGTTCCCAATCACTATATTGCAATCCCTGAGTGGTTTCTGTGCGAAAAT
GCCACGGTGGCTGCCGAGACCAGAGCAGTCATAGCCTGGATGGAAAAAATCCCTTTTGTGCT
GGGCGGCAACCTGCAGGGCGGCGAGCTGGTGGTGGCGTATCCCTACGACCTGGTGCGGTCCC
CCTGGAAGACGCAGGAACACACCCCCACCCCGATGACCACGTGTTCCGCTGGCTGGCCTAC
TCCTATGCCTCCACACACCGCCTCATGACAGACGCGCGGAGGAGGGTGTGCCACACGGAGGA
CTTCAGAAGGAGGAGGGCACTGTCAATGGGGCCTCCTGGCACACCGTCGCTGGAAGTCTGA
ACGATTTAGCTACCTTCATACAACTGCTTCGAAGTGTCCATCTACGTGGGCTGTGATAAA
TACCCACATGAGAGCCAGCTGCCCCGAGGAGTGGGAGAATAACCGGGAATCTCTGATCGTGTT
CATGGAGCAGGTTTCATCGTGGCATTAAAGGCTTGGTGAGAGATTACATGGAAAAGGAATCC
CAAACGCCATTATCTCCGTAGAAGGCATTAACCATGACATCCGAACAGCCAACGATGGGGAT
TACTGGCGCCTCCTGAACCTGGAGAGTATGTGGTCACAGCAAAGGCCGAAGGTTTCACTGC
ATCCACCAAGAACTGTATGGTTGGCTATGACATGGGGGCCACAAGGTGTGACTTCACACTTA
GCAAAACCAACATGGCCAGGATCCGAGAGATCATGGAGAAGTTTGGGAAGCAGCCCGTCAGC
CTGCCAGCCAGGCGGCTGAAGCTGCGGGGGCGGAAGAGACGACAGCGTGGGTGACCCCTCCTG
GGCCCTTGAGACTCGTCTGGGACCCATGCAAATTAACCAACCTGGTAGTAGCTCCATAGTG
GACTCACTCACTGTTGTTTCTCTGTAATTCAAGAAGTGCCTGGAAGAGAGGGTGCATTGTG
AGGCAGGTCCCAAAAGGGAAGGCTGGAGGCTGAGGCTGTTTTCTTTCTTTGTTCCATTATA
TCCAAATAACTTGGACAGAGCAGCAGAGAAAAGCTGATGGGAGTGAGAGAACTCAGCAAGCC
AACCTGGGAATCAGAGAGAGAAGGAGAAGGAGGGGAGCCTGTCCGTTAGAGCCTCTGGCTGC

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FIGURE 35B

ATAGAAAAGGATTCTGGTGCTTCCCCTGTTTGCGTGGCAGCAAGGGTTCACGTGCATTTGC
AATTTGCACAGCTAAAATTGCAGCATTTCCCCAGCTGGGCTGTCCCAAATGTTACCATTTGA
GATGCTCCCGGCGTCCTAAGAGAATCCACCCTCTCTGGCCCTGGGACATTGCAAGCTGCTA
CAAATAAATTCTGTGTTCTTTTGACAATAGCGTCATTGCCAAGTGCACATCAGTGAGCCTCT
TGAATCTGTTTAGTCTCCTTTTTCAACAAAGGAGTGTGTTCAGAAAAGGAGAGAGAGGCTGA
GATCATTGAGGAGTTTGTGGGCAGCAAGCATGGAGCTTCTTGACAAAATTCTGGGTCCATA
AACAAACCCCAAAGTCCCTGCTGATCCAGTAGCCCTGGAGGTTCCCCAGGTAGGGAGAGCCA
GAGGTGCCAGCCTTCCTGAAGGGCCAGAAAATTTAGCCTGGATCTCCTCTTTTACCTGCTAG
GACTGGAAAGAGCCAGAAGTGGGGTGGCCTGAAGCCCTCTCTCTGCTTGAGGTATTGCCCCCT
GTGTGGAATTGAGTGCTCATGGGTTGGCCTCATATCAGCCTGGGAGTTATTTTGTATATGTA
GAATGCCAGATCTTCCAGATTAGGCTAAATGTAATGAAAACCTCTTAGGATTATCTGTGGAG
CATCAGTTTGGAAGAATTATTGAATTATCTTGCAAGAAAAAAGTATGTCTCACTTTTTGTT
AATGTTGCTGCCTCATTGACCTGGGAAAAATGAAAAAAAAAATAAAGCAAATGGTAAGACC
CTTAAA

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FIGURE 36

MSRPGTATPALALVLLAVTLAGVGAQGALEDPDYYGQEIWSREPYARPEPELETFSPPLP
AGPGEEWERRPQEPRPPKRATKPKKAPKREKSAPEPPPPGKHSNKKVMRTKSSEKAANDDHS
VRVAREDVRESCPPLGLETLKITDFQLHASTVKRYGLGAHRGRLNIQAGINENDFYDGAWCA
GRNDLQQWIEVDARRLTRFTGVITQGRNSLWLSDWVTSYKVMVSNDSTWVTVKNGSGDMIF
EGNSEKEIPVLNELPVPMVARYIRINPQSWFDNGSICMRMEILGCPLPDPNNYYHRRNEMTT
TDDLDFKHHNYKEMRQLMKVVNEMCPNITRIYNIGKSHQGLKLYAVEISDHPGEHEVGEPEF
HYIAGAHGNEVLGRELLLLLVQFVCQEYLARNARIVHLVEETRIHVLPSLNPDGYEKAYEGG
SELGGWSLGRWTHDGIDINNNFPDLNTLLWEAEDRQNVPRKVPNHYIAIPEWFLSENATVAA
ETRAVIAWMEKIPFVLGGNLQGGELVVAYPYDLVRS PWKTQEHTPTPDDHVFRWLAYSAST
HRLMTDARRRVCHTEDFQKEEGTVNGASWHTVAGSLNDFSYLHTNCFELSIIYVGCDKYPHES
QLPEEWENNRESLIVFMEQVHRGIKGLVRDSHGKGI PNAIISVEGINHDIRTANDGDYWRLL
NPGEYVVTAKAEGFTASTKNCMVGYDMGATRCDFTL SKTNMARI REIMEKFGKQPVSLPARR
LKLGRKRQRG

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FIGURE 37

CTAAGAGGACAAGATGAGGCCCGCCTCTCATTTCTCCTAGCCCTTCTGTTCTTCCTTGGCC
AAGCTGCAGGGGATTTGGGGGATGTGGGACCTCCAATTCAGCCCCGGCTTCAGCTCTTTC
CCAGGTGTTGACTCCAGCTCCAGCTTCAGCTCCAGCTCCAGGTCCGGCTCCAGCTCCAGCCG
CAGCTTAGGCAGCGGAGGTTCTGTGTCCCAGTTGTTTTCCAATTTACCCGGCTCCGTGGATG
ACCGTGGGACCTGCCAGTGCTCTGTTTTCCCTGCCAGACACCACCTTTCCCGTGGACAGAGTG
GAACGCTTGGAATTCACAGCTCATGTTCTTTCTCAGAAAGTTTGAGAAAGAACTTTCTAAAGT
GAGGGAATATGTCCAATTAATTAGTGTGTATGAAAAGAACTGTTAAACCTAACTGTCCGAA
TTGACATCATGGAGAAGGATACCATTTCTTACACTGAACTGGACTTCGAGCTGATCAAGGTA
GAAGTGAAGGAGATGGAAAACTGGTCATACAGCTGAAGGAGAGTTTTGGTGGAAGCTCAGA
AATTGTTGACCAGCTGGAGGTGGAGATAAGAAATATGACTCTCTTGGTAGAGAAGCTTGAGA
CACTAGACAAAAACAATGTCCTTGCCATTCGCCGAGAAATCGTGGCTCTGAAGACCAAGCTG
AAAGAGTGTGAGGCCTCTAAAGATCAAAACACCCCTGTCTGCCACCCCTCTCCCACTCCAGG
GAGCTGTGGTCAATGGTGGTGTGGTGAACATCAGCAAACCGTCTGTGGTTCAGCTCAACTGGA
GAGGGTTTTCTTATCTATATGGTGCTTGGGGTAGGGATTACTCTCCCCAGCATCCAAACAAA
GGACTGTATTGGGTGGCGCCATTGAATACAGATGGGAGACTGTTGGAGTATTATAGACTGTA
CAACACACTGGATGATTTGCTATTGTATATAAATGCTCGAGAGTTGCGGATCACCTATGGCC
AAGGTAGTGGTACAGCAGTTTACAACAACAACATGTACGTCAACATGTACAACACCGGGAAT
ATTGCCAGAGTTAACCTGACCACCAACACGATTGCTGTGACTCAAACCTCTCCCTAATGCTGC
CTATAATAACCGCTTTTCATATGCTAATGTTGCTTGGCAAGATATTGACTTTGCTGTGGATG
AGAATGGATTGTGGGTTATTTATTCAACTGAAGCCAGCACTGGTAACATGGTGATTAGTAAA
CTCAATGACACCACACTTCAGGTGCTAAACACTTGGTATACCAAGCAGTATAAACCATCTGC
TTCTAACGCCTTCATGGTATGTGGGGTTCTGTATGCCACCCGTAATATGAACACCAGAACAG
AAGAGATTTTTTACTATTATGACACAAACACAGGGAAAGAGGGCAAACCTAGACATTGTAATG
CATAAGATGCAGGAAAAAGTGCAGAGCATTAACCTATAACCCTTTTGACCAGAACTTTATGT
CTATAACGATGGTTACCTTCTGAATTATGATCTTTCTGTCTTGCAGAAGCCCCAGTAAGCTG
TTTAGGAGTTAGGGTGAAAGAGAAAATGTTTGTGTAAGAAAATAGTCTTCTCCACTTACTTAG
ATATCTGCAGGGGTGTCTAAAAGTGTGTTCAATTTTGCAGCAATGTTTAGGTGCATAGTTCTA
CCACACTAGAGATCTAGGACATTTGTCTTGATTTGGTGAGTTCTCTTGGGAATCATCTGCCT
CTTCAGGCGCATTTTGCATAAAGTCTGTCTAGGGTGGGATTGTGAGAGGTCTAGGGGCACT
GTGGGCCTAGTGAAGCCTACTGTGAGGAGGCTTCACTAGAAGCCTTAAATTAGGAATTAAGG
AACTTAAACTCAGTATGGCGTCTAGGGATTCTTTGTACAGGAAATATTGCCAATGACTAG
TCCTCATCCATGTAGCACCCTAATTCTTCATGCCTGGAAGAAACCTGGGGACTTAGTTAG
GTAGATTAAATATCTGGAGCTCCTCGAGGGACCAATCTCCAACCTTTTTTTCCCTCACTAG
CACCTGGAATGATGCTTTGTATGTGGCAGATAAGTAAATTTGGCATGCTTATATATTCTACA
TCTGTAAAGTGCTGAGTTTTATGGAGAGAGGCCTTTTTATGCATTAAATTGTACATGGCAAA
TAAATCCCAGAAGGATCTGTAGATGAGGCACCTGCTTTTTCTTTTCTCTCATTGTCCACCTT
ACTAAAAGTCAGTAGAATCTTCTACCTCATAACTTCCTTCAAAGGCAGCTCAGAAGATTAG
AACCAGACTTACTAACCAATTCCACCCCCACCAACCCCTTCTACTGCCTACTTTAAAAAA
ATTAATAGTTTTCTATGGAACCTGATCTAAGATTAGAAAAATTAATTTTCTTTAATTTTCTTA
TGGACTTTTATTTACATGACTCTAAGACTATAAGAAAATCTGATGGCAGTGACAAAGTGCTA
GCATTTATTGTTATCTAATAAAGACCTTGGAGCATATGTGCAACTTATGAGTGTATCAGTTG
TTGCATGTAATTTTTGCCTTTGTTTAAAGCCTGGAACCTGTAAGAAAATGAAAATTTAATTTT
TTTTTCTAGGACGAGCTATAGAAAAGCTATTGAGAGTATCTAGTTAATCAGTGCAGTAGTTG
GAAACCTTGCTGGTGTATGTGATGTGCTTCTGTGCTTTTGAATGACTTTATCATCTAGTCTT
TGTCTATTTTTCTTTTGATGTTCAAGTCCTAGTCTATAGGATTGGCAGTTTAAATGCTTTAC
TCCCCCTTTTAAATAAATGATTAAATGTGCTTTGAAAAAATAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 38

MRPGLSFLLALLFFLGQAAGDLGDVGPPIPSPGFSSFPGVDSSSSFSSSSSRSGSSSSRSLGS
GGSVSQLFSNFTGSVDDRGTQCQSVSLPDTTFPVDRVERLEFTAHVLSQKFEKELSKVREYV
QLISVYEKKLLNLTVRIDIMEKDTISYTELDFELIKVEVKEMEKLVIQLKESFGGSSEIVDQ
LEVEIRNMTLLVEKLETLDKNNVLAIRREIVALKTKLKECEASKDQNTPVVHPPPTPGSCGH
GGVVNISKPSVVQLNWRGFSYLYGAWGRDYSPQHHPNKGLYWVAPLNTDGRLLLEYRLYNTLD
DLLLYINARELRITYGQSGTAVYNNNMYVNMYNTGNIARVNLTTNTIAVTQTLPNAAAYNNR
FSYANVAWQDIDFAVDENGLWVIYSTEASTGNMVISKLNDTTLQVLNTWYTKQYKPSASNAF
MVCGLVLYATRTMNRTEEIFYYYDTNTGKEGKLIVMHKMQEKVQSINYNPFDQKLYVYNDG
YLLNYDLSVLQKPQ

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FIGURE 39

GCTCTGAAGACCAAGCTGAAAGAGTGTGAGGCCTCTAAAGATCAAACACCCCTGTCGTCCAC
CCTCCTCCCCTCCAGGGAGCTGTGGTCATGGTGGTGTGGTGAACATCAGCAAACCGTCTGT
GGTTCAGCTCAACTGGAGAGGGTTTTCTTATCTATATGGTGCTTGGGGTAGGGATTACTCTC
CCCAGCATCCAAACAAAGGNATGTATTGGGNGGCGCCATTGAATACAGATGGGAGACTGTTG
GAGTATTATAGACTGTACAACCCACTGGATGATTGCTATTGTATATAAATGCTCGAGAGTT
GCGGATCACCTATGGCCAAGGTAGTGGTACAGCAGTTTACAACAACAACATGTACGTCAACA
TGTACAACACCGGNATATTGCCAGAGTTAACCTGACC

FIGURE 40

TCTCGCAGATAGTAAATAATCTCGGAAAGGCGAGAAAGAAGCTGTCTCCATCTTGTCTGTAT
CCGCTGCTCTTGTGACGTTGTGGAGATGGGGAGCGTCCTGGGGCTGTGCTCCATGGCGAGCT
GGATACCATGTTTGTGTGGAAGTGCCCCGTGTTTGTCTATGCCGATGCTGCTCCTAGTGGAAC
AACTCCACTGTAAGTAGATTGATCTATGCACCTTTCTTGCTTGTGGAGTATGTGTAGCTTG
TGTAATGTTGATACCAGGAATGGAAGAACAAGTGAATAAGATTCTTGGAATTTGTGAGAATG
AGAAAGGTGTTGTCCCTTGTAAACATTTTGGTTGGCTATAAAGCTGTATATCGTTTGTGCTTT
GGTTTGGCTATGTTCTATCTTCTTCTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGA
TCCTAGAGCTGCAGTGCACAATGGATTTTGGTTCTTTAAATTTGCTGCAGCAATTGCAATTA
TTATTGGGGCATTTCTTCATCCAGAAGGAACCTTTTACAAGTGTGTGGTTTTATGTAGGCATG
GCAGGTGCCTTTTGTTCATCCTCATACAAGTCTTACTTATTGATTTTGCACATTCATG
GAATGAATCGTGGGTTGAAAAAATGGAAGAAGGGAAGTCTGAGATGTTGGTATGCAGCCTTGT
TATCAGCTACAGCTCTGAATTATCTGCTGTCTTTAGTTGCTATCGTCCTGTTCTTTGTCTAC
TACACTCATCCAGCCAGTTGTTTCAAGAAACAAGGCGTTCATCAGTGTCAACATGCTCCTCTG
CGTTGGTGCTTCTGTAAATGTCTATACTGCCAAAAATCCAAGAATCACAAACCAAGATCTGGTT
TGTTACAGTCTTCAGTAATTACAGTCTACACAATGTATTTGACATGGTCAGCTATGACCAAT
GAACCAGAAACAAATTGCAACCCAAGTCTACTAAGCATAATTGGCTACAATACAACAAGCAC
TGTCCCAAAGGAAGGGCAGTCAGTCCAGTGGTGGCATGCTCAAGGAATTATAGGACTAATTC
TCTTTTGTGTGTATTTTATTCCAGCATCCGTACTTCAAACAATAGTCAGGTTAATAAA
CTGACTCTAACAAGTGATGAATCTACATTAATAGAAGATGGTGGAGCTAGAAGTGATGGATC
ACTGGAGGATGGGGACGATGTTCAACGAGCTGTAGATAATGAAAGGGATGGTGTCACTTACA
GTTATTCCTTCTTTCATTTTCTGCTTTTCTGCTTCACTTTATATCATGATGACCCTTACC
AACTGGTCCAGGTATGAACCCTCTCGTGAGATGAAAAGTCAGTGGACAGCTGTCTGGGTGAA
AATCTCTTCCAGTTGGATTGGCATCGTGTGTATGTTTGGACACTCGTGGCACCCTTGTTC
TTACAAATCGTGATTTTGAAGTGAAGTCTAGCATGAAAGTCCCCTTTGATTATTGC
TTATTTGAAAACAGTATTCCCAACTTTTGTAAAGTTGTGTATGTTTTGCTTCCCATGTAA
TTCTCCAGTGTTCTGGCATGAATTAGATTTTACTGCTTGTCAATTTGTTATTTTCTTACCAA
GTGCATTGATATGTGAAGTAGAATGAATTGCAGAGGAAAGTTTTATGAATATGGTGATGAGT
TAGTAAAAGTGGCCATTATTGGGCTTATTCTGCTCTATAGTTGTGAAATGAAGAGTAAAA
ACAAATTTGTTGACTATTTTAAAATTATATTAGACCTTAAGCTGTTTGTAGCAAGCATTA
GCAAATGTATGGCTGCCTTTTGAATATTTGATGTGTTGCCTGGCAGGATACTGCAAGAAC
ATGGTTTATTTTAAAATTTATAAACAAGTCACTTAAATGCCAGTTGTCTGAAAAATCTTATA
AGGTTTTACCCTTGATACGGAATTTACACAGGTAGGGAGTGTTTAGTGGACAATAGTGTAGGTTA
TGGATTGGAGGTGTCGGTACTAAATTGAATAACGAGTAAATAATCTTACTTGGGTAGAGATGG
CCTTTGCCAACAAAGTGAAGTGTGTTTGGTTGTTTTAACTCATGAAGTATGGGTTTCAAGTGA
AATGTTTGGAACTCTGAAGGATTTAGACAAGGTTTTGAAAAGGATAATCATGGGTTAGAAGG
AAGTGTGTTTGAAGTCACTTTGAAAGTTAGTTTTGGGCCCAGCACGGTAGCTCACCTTGGT
AATCCCAGCACTTTGGGAGCTTAAGTGGGTAGATTACTTGAGCCCAGGAATTCAGACCAGCT
TGGCACATGGTGAACCTGTTCTATAAAAAATAATCTGGCTTTGAGCATATGCCTGTGGTCCAG
CACTGAGAGGCTAGTGAAGATTGCTGAGCCCAGAGCCAAAGGTTGCAGTGAGCAAGTCACGT
CACTGCACTCTAGCTGGCACAGAGTAAGCCAAAAAATATATATATATTGAAATCAAGGAGG
CAAAATTTTGAAGGGAAGGAAGTAACTGCAAAACCACTAGGCTTTAGTAGGTACTTATATA
AAATCTAGTCCAGTTCTCTCATTTAAAAAATGAAGACACTGAAATACAGACTTAAATAGCT
CAGATAGCTAATTAGGAAATTTCAAGTTGGCCAATAATAGCATTCTCTGACATTTAAAAA
TAATTTCTATTCAAATACATGCATATTGATTTACACCTCATACTGTGATAATTAATGTGAT
GTGGATTGCTGGTGTCCAGCATGACCATAAACAGGTGAGAAGAATGATGGAATGTTTTAGA
ATAAATCCTGCTTATAGTATACTACACAGTTCAAAAGATGTTTAAAAATGCTTTTGTATTTA
CTGCCATGTAATTGAAATATATAGATTATTGTAACCTTTCAACCTGAAAAATCAAGCAGTATG
AGAGTTTAGTTATTTGTATGTGTCACTAGTGTCTAATGAAGCTTTTAAATCTACAATTTCT
TCTTTAAAAATATTTATTAATGTGAATGGAATATAACAATTCAGCTTAATTCCTCAACCTTA
TTCTGTGTGTAGACATTGTATTCACAATTTGAATGGCTGTGTTTACCTCTAAATAAATG
AATTCAGAGAAAAA

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FIGURE 41

MGSVLGLCSMASWIPCLCGSAPCLLCRCCPSGNNSTVTRLIYALFLLVGVCVACVMLIPGME
EQLNKIPGFCENEKGVVPCNILVGKYKAVYRLCFGLAMFYLLLSLLMIKVKSSSDPRAAVHNG
FWFFKFAAAIAIIIGAFFIPEGTFTTVWFYVGMAGAFCFILIQVLVLLIDFAHSWNESWVEKM
EEGNSRCWYAALLSATALNYLLSLVAIVLFFVYYTHPASCSSENKAFISVNMLLCVGASVMSI
LPKIQESQPRSGLLQSSVITVYTMYLTSAMTNEPETNCNPSLLSIIGYNTTSTVPKEGQSV
QWWHAQGIIGLILFLLCVFYSSIRTSNNSQVNKLTLTSDESTLIEDGGARSDGSLEDGDDVH
RAVDNERDGVITYSYSFFHFMLFLASLYIMMTLTNWSRYEPSREMKSQWTAVVWKISSSWIGI
VLYVWTLVAPLVLTNRDFD

FIGURE 42

GCGAGAAAGAAGCTGTCTCCATCTTGTCTGTATCCCGCTGCTTCTTGNGACGTTGTGGAGAT
GGGGAGCGTCCCTGGGGCTGTGCTCCATGGCGAGCTGGATACCATGTTTGTGTGGAAGTGCC
CCGTGTTTGCTATGCCGATGCTGTCCTAGTGGAACAANTCCACTGTAAC TAGATTGATCTA
TGCACTTTTCTTGCTTGTTGGAGTATGTGTAGCTTGTGTAATGTTGATACCAGGAATGGAAG
AACAACTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAGGTGTTGTCCTTGTAACATT
TTGGTTGGCTATAAAGCTGTATATCGTTTGTGCTTTGGTTGGCTATGTTCTATCTTCTTCT
CTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCAGTGCACAATGGAT
TTTGGTTCTTTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGC

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FIGURE 43

GTTATTGTGAACTTTGTGGAGATGGGAGGTCNTGGGGCTGTGTTCCATGGCGAGCTGGATAC
CANGTTTGTGTGGAAGTGCCCCGTGTTTGNATGCCGATGCTGTCCTAGTGGAACAANTCC
ACTGTAATTAGATTGATNTATGCACTTTTNTTGCTTGTGGAGTANGTGTAGCTTGTGTAAT
GTTGATACCAGGAATGGAAGAACAACCTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAG
GTGTTGTCCCTTGTAACATTTTGGTTGGCTATAAAGCTGTATATNGTTTGTGCTTTGGTTTG
GCTANGTTCTATNTTCTTCTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAG
AGCTGCAGTGCACAATGGATTTTGGTTTTTTAAATTTGCTGCAGCAATTGCAATTATTATTG
GGGC

FIGURE 44

AAGAAGCTGTCTCCATCTTGTCTGTATCCGCTGCTCTTGTGAACGTTNTGGAGATGGGGAGC
GTCCTTGGGGTTGTGCTCCATGGCGAGCTGGATAACCATGTTTGTGTGGAAGTGCCCCGTGTT
TGCTATGCCGATGCTGTCCTAGTGGAACAACCTCCACTGTAACTAGATTGATCTATGCACTT
TTCTTGCTTGTTGGAGTATGTGTAGCTTGTGTAATGTTGATACCAGGAATGGAAGAACAACCT
GAATAAGATTCCTGGATTTTGTGAGAATGAGAAAGGTGTTGTCCCTTGTAACATTTTGGTTG
GCTATAAAGCTGTATATCGTTTGTGCTTTGGTTTGGCTATGTTCTATCTTCTTCTCTTTA
CTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCAGTGCACAATGGATTTTGGTT
CTTTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGC

FIGURE 45

GCTGTCCTTAGTGGAACAANTCCAACCTTGTAACCTTGGATTGATCTATGCACTTTTTCCTTG
CTTGTTGGAGTATGTGTAGCTTTGTGTAATGTTGTTCCCAGGATTGGANGAACAACTGAATA
AGATTCCTGGATTTTTGTGAGAATGAGAAAGGTGTTGTCCCCTTGTAACATTTTTGGTTGGC
TATAAAGCTGTATATCGTTTGTGCTTTGGTTTGGCTATGTTCTATCTTCTTCTCTCTTTACT
AATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCAGTGCACAATGGATTTTGGTTCT
TTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGCATTCTTCATTCCAGAAGGAACCTTT
ACAACTGTGTGGTTTTATGTAGGCATGGCAGGTGCCTTTTGTTCATCCTCATACTAGT
CTTACTTATTGATTTTGCACATTCATGGAATGAATCGTGGGTGAAAAAATGGAAGAAGGGA
ACTCGAGATGTTGGTATGCAGCCTTGTTATCAGCTACAGCTCTGAATTATCTGCTGTCTTTA
GTTGCTATCGTCCTGTTCTTTGTCTACTACACTCATCCAGCCAGTTGTTTCAGAAAACAAGGC
GTTTCATCAGTGTCAACATGCTCCTCTGCGTTGGTGCTTCTGTAATG

FIGURE 46A

CTCGGGCGCGCACAGGCAGCTCGGTTTGCCCTGCGATTGAGCTGCGGGTCGCGGCCGGCGCC
GGCCTCTCCAATGGCAAATGTGTGTGGCTGGAGGCGAGCGGAGGCTTTTCGGCAAAGGCAGT
CGAGTGTTCAGACCGGGGCGAGTCCTGTGAAAGCAGATAAAAGAAAACATTTATTAACGT
GTCATTACGAGGGGAGCGCCCGGCCGGGGCTGTGCGACTCCCCGCGGAACATTTGGCTCCCT
CCAGCTCCGAGAGAGGAGAAGAAGAAAGCGGAAAAGAGGCAGATTACGTCGTTTCCAGCCA
AGTGGACCTGATCGATGGCCCTCCTGAATTTATCACGATATTTGATTTATTAGCGATGCCCC
CTGGTTTGTGTGTTACGCACACACACGTGCACACAAGGCTCTGGCTCGCTTCCCTCCCTCGT
TTCCAGCTCCTGGGCGAATCCCACATCTGTTTCAACTCTCCGCCGAGGGCGAGCAGGAGCGA
GAGTGTGTGCAATCTGCGAGTGAAGAGGGACGAGGGAAGAAACAAAGCCACAGACGCAAC
TTGAGACTCCCGCATCCCAAAAGAAGCACCAGATCAGCAAAAAAAGAAGATGGGGCCCCCGA
GCCTCGTGCTGTGCTTGCTGTCCGCAACTGTGTTCTCCCTGCTGGGTGGAAGCTCGGCCTTC
CTGTGCGACCACCGCCTGAAAGGCAGGTTTCAGAGGGACCGCAGGAACATCCGCCCAACAT
CATCCTGGTGCTGACGGACGACCAGGATGTGGAGCTGGGTTCCATGCAGGTGATGAACAAGA
CCCGGCGCATCATGGAGCAGGGCGGGGCGCACTTCATCAACGCCTTCGTGACCACACCCATG
TGCTGCCCCCTCACGCTCCTCCATCCTCACTGGCAAGTACGTCCACAACCACAACACCTACAC
CAACAATGAGAACTGCTCCTCGCCCTCCTGGCAGGCACAGCACGAGAGCCGCACCTTTGCCG
TGTACCTCAATAGCACTGGCTACCGGACAGCTTTCTTCGGGAAGTATCTTAATGAATACAAC
GGCTCCTACGTGCCACCCGGCTGGAAGGAGTGGGTGCGACTCCTTAAAACTCCCGCTTTTA
TAACTACACGCTGTGTGCGAACGGGGTGAAAGAGAAGCACGGCTCCGACTACTCCAAGGATT
ACCTCACAGACCTCATCACCATGACAGCGTGAGCTTCTTCCGCACGTCCAAGAAGATGTAC
CCGCACAGGCCAGTCCTCATGGTCATCAGCCATGCAGCCCCCAGGGCCCTGAGGATTCAGC
CCCACAATATTCACGCCTCTTCCCAAACGCATCTCAGCACATCACGCCGAGCTACAACCTACG
CGCCCAACCCGGACAAACACTGGATCATGCGCTACACGGGGCCCATGAAGCCCATCCACATG
GAATTACCAACATGCTCCAGCGGAAGCGCTTGACAGCCCTCATGTGGTGGACGACTCCAT
GGAGACGATTTACAACATGCTGGTTGAGACGGGCGAGCTGGACAACACGTACATCGTATACA
CCGCCGACCACGGTTACCACATCGGCCAGTTTGGCCTGGTGAAAGGGAAATCCATGCCATAT
GAGTTTGACATCAGGGTCCCGTTCTACGTGAGGGGCCCCAACGTGGAAGCCGGCTGTCTGAA
TCCCCACATCGTCCTCAACATTGACCTGGCCCCCACCATCCTGGACATTGCAGGCCTGGACA
TACCTGCGGATATGGACGGGAAATCCATCCTCAAGCTGCTGGACACGGAGCGGCCGGTGAAT
CGGTTTCACTTGAAAAAGAAGATGAGGGTCTGGCGGGACTCCTTCTTGGTGGAGAGAGGCAA
GCTGCTACACAAGAGAGACAATGACAAGGTGGACGCCAGGAGGAGAACTTTCTGCCCAAGT
ACCAGCGTGTGAAGGACCTGTGTGACGCTGTGAGTACCAGACGGCGTGTGAGCAGCTGGGA
CAGAAGTGGCAGTGTGTGGAGGACGCCACGGGGAAGCTGAAGCTGCATAAGTGCAAGGGCCC
CATGCGGCTGGGCGGCAGCAGAGCCCTCTCAACCTCGTGCCCAAGTACTACGGGCAGGGCA
GCGAGGCTGACCTGTGACAGCGGGGACTACAAGCTCAGCCTGGCCGGACGCCGGAACAAA
CTCTTCAAGAAGAAGTACAAGGCCAGCTATGTCCGCAGTCGCTCCATCCGCTCAGTGGCCAT
CGAGGTGGACGGCAGGGTGTACCACGTAGGCCTGGGTGATGCCGCCAGCCCCGAAACCTCA
CCAAGCGGCACTGGCCAGGGGCCCTGAGGACCAAGATGACAAGGATGGTGGGGACTTCAGT
GGCACTGGAGGCCTTCCCGACTACTCAGCCGCCAACCCATTAAAGTGACACATCGGTGCTA
CATCCTAGAGAACGACACAGTCCAGTGTGACCTGGACCTGTACAAGTCCCTGCAGGCCTGGA
AAGACCACAAGCTGCACATCGACCACGAGATTGAAACCCTGCAGAACAAAATTAAGAACCTG
AGGGAAGTCCGAGGTACCTGAAGAAAAAGCGGCCAGAAGAATGTGACTGTACAAAATCAG
CTACCACACCCAGCACAAAGGCCGCTCAAGCACAGAGGCTCCAGTCTGCATCCTTTTCAGGA
AGGGCCTGCAAGAGAAGGACAAGGTGTGGCTGTTGCGGGAGCAGAAGCGCAAGAAGAACTC
CGCAAGCTGCTCAAGCGCCTGCAGAACACGACACGTGCAGCATGCCAGGCCTCACGTGCTT
CACCCACGACAACCAGCACTGGCAGACGGCGCCTTTCTGGACACTGGGGCCTTTCTGTGCCT
GCACCAGCGCAACAATAACACGTACTGGTGCATGAGGACCATCAATGAGACTCACAATTTT

FIGURE 46B

CTCTTCTGTGAATTTGCAACTGGCTTCCTAGAGTACTTTGATCTCAACACAGACCCCTACCA
GCTGATGAATGCAGTGAACACACTGGACAGGGATGTCCTCAACCAGCTACACGTACAGCTCA
TGGAGCTGAGGAGCTGCAAGGGTTACAAGCAGTGTAACCCCCGGAAGTGGCCAGAAATGAAGAG
GATGGAGGAAGCTATGAGCAATACAGGCAGTTTCAGCGTCGAAAGTGGCCAGAAATGAAGAG
ACCTTCTTCCAAATCACTGGGACAACGTGTGGGAAGGCTGGGAAGGT**TA**AAGAAACAACAGAGG
TGGACCTCCAAAAACATAGAGGCATCACCTGACTGCACAGGCAATGAAAAACCATGTGGGTG
ATTTCCAGCAGACCTGTGCTATTGGCCAGGAGGCCTGAGAAAGCAAGCACGCACTCTCAGTC
AACATGACAGATTCTGGAGGATAACCAGCAGGAGCAGAGATAACTTCAGGAAGTCCATTTTT
GCCCCTGCTTTTGCTTTGGATTATACCTCACCAGCTGCACAAAATGCATTTTTTCGTATCAA
AAAGTCACCACTAACCCTCCCCCAGAAGCTCACAAAGGAAAACGGAGAGAGCGAGCGAGAGA
GATTTCTTGGAATTTCTCCCAAGGGCGAAAGTCATTGGAATTTTTAAATCATAGGGGAAA
AGCAGTCCTGTTCTAAATCCTCTTATTCTTTTGGTTTGTACAAAGAAGGAACCTAAGAAGCA
GGACAGAGGCAACGTGGAGAGGCTGAAAACAGTGCAGAGACGTTTGACAATGAGTCAGTAGC
ACAAAAGAGATGACATTACCTAGCACTATAAACCCCTGGTTGCCTCTGAAGAACTGCCTTC
ATTGTATATATGTGACTATTTACATGTAATCAACATGGGAACTTTtaggggaacctaataag
AAATCCCAATTTTCAGGAGTGGTGGTGTCAATAAACGCTCTGTGGCCAGTGTAAGAAAAA

FIGURE 47

MGPPSLVLCLLSATVFSLLGGSSAFLSHHRLKGRFQDRRNIRPNIILVLTDDQDVELGSMQ
VMNKTRRIMEQGGAHFINAFVTTPMCCPSRSSILTGKYVHNHNTYTNNECSPSWQAQHE
RTFAVYLNSTGYRTAFFGKYLNEYNGSYVPPGWKEWVGLLKNSRFYNYTLCRNGVKEKHGSD
YSKDYLTDLITNDSVSFFRTSKKMYPHRPVLMVISHAAPHGPEDSAPQYSRLFPNASQHITP
SYNYAPNPDKHWIMRYTGPMKPIHMEFTNMLQRKRLQTLMSVDDSMETIYNMLVETGELDNT
YIVYTADHGYHIGQFGLVKGKSMPEYFDIRVPFYVRGPNVEAGCLNPHIVLNIDLAPTILDI
AGLDIPADMKGKSILKLLDTERPVNRFHLKKKMRVWRDSFLVERGKLLHKRDNDKVDAQEEN
FLPKYQRVKDLQRAEYQTACEQLGQKWQCVEDATGKLLKHKCKGPMRLGGSRALSNLVPKY
YGQGSEACTCDSDYKLSLAGRRKKLFKKKYKASYVRSRSIRSVAI EVDGRVYHVGLGDAAQ
PRNLTKRHWP GAPEDQDDKDGGDFSGTGGLPDYSAANPIKVTHRCYILENDTVQCDLDLYKS
LQAWKDHKLHIDHEIETLQNKIKNLREVRGHLKKKRPEECDCHKISYHTQHKGRCLKHRGSSL
HPFRKGLQEKDKVWLLREQKRKKKLRKLLKRLQNNDTCSMPGLTCFTHDNQHWQTAPFWTLG
PFCACTSANNNTYWC MRTINETHNFLFCE FATGFLEYFDLNTDPYQLMNAVNTLDRDVLNQL
HVQLMELRSCKGYKQCNPRTRNMDLDGGSYEQYRQFQRRKWPEMKRPSSKSLGQLWEGWEG

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FIGURE 48

AACAAAGTTCAGTGA CTGAGAGGGCTGAGCGGAGGCTGCTGAAGGGGAGAAAGGAGTGAGGA
GCTGCTGGGCAGAGAGGGACTGTCCGGCTCCAGATGCTGGGCCTCCTGGGGAGCACAGCCC
TCGTGGGATGGATCACAGGTGCTGCTGTGGCGGTCTGCTGCTGCTGCTGCTGCTGCTGGCCACC
TGCCTTTTCCACGGACGGCAGGACTGTGACGTGGAGAGGAACCGTACAGCTGCAGGGGGAAA
CCGAGTCCGCCGGGCCCAGCCTTGGCCCTTCCGGCGGGGGCCACCTGGGAATCTTTCACC
ATCACCGTCATCCTGGCCACGTATCTCATGTGCCGAATGTGGGCCTCCACCACCACCACCAC
CCCCGCCACACCCCTCACCACCTCCACCACCACCACCACCCCCACCGCCACCATCCCCGCCA
CGCTCGCTTGAGGCTGCTGTGCGCGGTGCCTGTGGACAGCAGCTGCCCCCTGCCCTCCCATCTG
TTCCCAGGACAAGTGGACCCCATGTTTCCATGTGGAAGGATGCATCTCTGGGGTGAACGAGG
GGAACAATAGACTGGGGCTTGCTCCAGCTGCATTTGCATGGCATGCCCCAGTGTACTATGGC
AGCAGAGAATGGAGGAACACTGGGTCTGCAGTGCTGAAGGGTTTGGGGAGTGGAGAGCAAGG
GTGCTCTTTCGGGGCTGGACAGCCCGTCTTGTGACAGTGACTCCCAGTGAGCCCCAGAAATG
ACAAGCGTGTCTTGGCAGAGCCAGCACACAAGTGGATGTGAAGTGCCCGTCTTGACCTCCTC
ATCAGGCTGCTGCAGGCCTCTGGCGGGCAGGGCACTGGGAGAGGCCCTGAGAATGTCCTTTT
GGTTTGGAGAAGGCAGTGTGAGGCTGCACAGTCAATTCATCGGTGCCTTAGTCCAAGAAAAT
AAAAACCACTAAGAAGCTTTAAAAAAAAAAAAAAAAAAAAA

FIGURE 49

MLGLLGSTALVGWITGAAVAVLLLLLLLATCLFHGRQDCDVERNRTAAGGNRVRRAPWPFR
RRGHLGIFHHHRHPGHVSHVPNVGLHHHHHPRHTPHHLHHHHHPRHHPRHAR

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FIGURE 50

GGCGGCTGCTGAGCTGCCTTGAGGTGCAGTGTTGGGGATCCAGAGCCATGTCGGACCTGCTA
CTACTGGGCCTGATTGGGGCCTGACTCTCTTACTGCTGCTGACGCTGCTGGCCTTTGCCGG
GTACTCAGGGCTACTGGCTGGGGTGGAAGTGAGTGCTGGGTACCCCCCATCCGCAACGTCA
CTGTGGCCTACAAGTTCCACATGGGGCTCTATGGTGAGACTGGGCGGCTTTTCACTGAGAGC
TGCAGCATCTCTCCAAGCTCCGCTCCATCGCTGTCTACTATGACAACCCCCACATGGTGCC
CCCTGATAAGTGCCGATGTGCCGTGGGCAGCATCCTGAGTGAAGGTGAGGAATCGCCCTCCC
CTGAGCTCATCGACCTCTACCAGAAATTTGGCTTCAAGGTGTTCTCCTTCCCGGCACCCAGC
CATGTGGTGACAGCCACCTTCCCCTACACCACCATCTGTCCATCTGGCTGGCTACCCGCCG
TGTCCATCCTGCCTTGACACCTACATCAAGGAGCGGAAGCTGTGTGCCTATCCTCGGCTGG
AGATCTACCAGGAAGACCAGATCCATTTTCATGTGCCCACTGGCACGGCAGGGAGACTTCTAT
GTGCCTGAGATGAAGGAGACAGAGTGGAATGGCGGGGGCTTGTGGAGGCCATTGACACCCA
GGTGGATGGCACAGGAGCTGACACAATGAGTGACACGAGTTCTGTAAGCTTGGAAGTGAGCC
CTGGCAGCCGGGAGACTTCAGCTGCCACACTGTACCTGGGGCGAGCAGCCGTGGCTGGGAT
GACGGTGACACCCGCAGCGAGCACAGCTACAGCGAGTCAGGTGCCAGCGGCTCCTCTTTTGA
GGAGCTGGACTTGGAGGGCGAGGGGCCCTTAGGGGAGTCACGGCTGGACCCTGGGACTGAGC
CCCTGGGGACTACCAAGTGGCTCTGGGAGCCCACTGCCCCTGAGAAGGGCAAGGAGTAACCC
ATGGCCTGCACCCTCCTGCAGTGCAAGTTGCTGAGGAACTGAGCAGACTCTCCAGCAGACTCT
CCAGCCCTCTTCTCCTTCTCTGGGGGAGGAGGGGTTCTGAGGGACCTGACTTCCCCTGC
TCCAGGCCCTCTTGCTAAGCCTTCTCCTCACTGCCCTTTAGGCTCCAGGGCCAGAGGAGCCA
GGGACTATTTTCTGCACCAGCCCCCAGGGCTGCCGCCCTGTTGTGTCTTTTTTTCAGACTC
ACAGTGGAGCTTCCAGGACCCAGAATAAAGCCAATGATTTACTTGTTCACCTGGAAAAAAA
AAAAA

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FIGURE 51

MSDLLLLGLIGGLTLLLLLTLLAFAGYSGLLAGVEVSAGSPPIRNVTVAYKFHMGLYGETGR
LFTESCSISPKLRSIAVYYDNPHMVPPDKCRCAGVSILSEGEESPSPELIDLYQKFGFKVFS
FPAPSHVVTATFPYTTILSIWLATRRVHPALDTYIKERKLCAYPRLEIYQEDQIHFMCPAR
QGDFYVPEMKETEWKWRGLVEAIDTQVDGTGADTMSDTSSVSLEVSPGSRETSAAATLSPGAS
SRGWDDGDTRSEHSYSESGASCSSFEELDLEGEGLGESRLDPGTEPLGTTKWLWEPTAPEKGKE

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FIGURE 52

CCGCGGGAACGCTGTCCTGGCTGCCGCCACCCGAACAGCCTGTCCTGGTGCCCCGGCTCCCT
GCCCCGCGCCAGTCATGACCCTGCGCCCCCTCACTCCTCCCGCTCCATCTGCTGCTGCTGCT
GCTGCTCAGTGCGGCGGTGTGCCGGGCTGAGGCTGGGCTCGAAACCGAAAGTCCCGTCCGGA
CCCTCCAAGTGGAGACCCTGGTGGAGCCCCCAGAACCATGTGCCGAGCCCGCTGCTTTTGGA
GACACGCTTCACATACACTACACGGGAAGCTTGGTAGATGGACGTATTATTGACACCTCCCT
GACCAGAGACCCCTCTGGTTATAGAACTTGGCCAAAAGCAGGTGATTCCAGGTCTGGAGCAGA
GTCTTCTCGACATGTGTGTGGGAGAGAAGCGAAGGGCAATCATTCCTTCTCACTTGGCCTAT
GGAAAACGGGGATTTCCACCATCTGTCCCAGCGGATGCAGTGGTGCAGTATGACGTGGAGCT
GATTGCACTAATCCGAGCCAACTACTGGCTAAAGCTGGTGAAGGGCATTTTGCCTCTGGTAG
GGATGGCCATGGTGCCAGCCCTCCTGGGCCTCATTGGGTATCACCTATACAGAAAGGCCAAT
AGACCCAAAGTCTCCAAAAGAAGCTCAAGGAAGAGAAACGAAACAAGAGCAAAAAGAATA
ATAAATAATAAATTTTAAAAAACTTAAAAAAAAAAAAAAAAAAAA

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FIGURE 53

MTLRPSLLPLHLLLLLLLLSAAVCRAEAGLETESPVRTLQVETLVEPPEPCAEPAAFCDTLHI
HYTGSLVDGRIIDTSLTRDPLVIELGQKQVIPGLEQSLLDMCVGEKRRAIIPSHLAYGKRGF
PPSVPADAVVQYDVELIALIRANYWLKLVKGILPLVGMAMVPALLGLIGYHLYRKANRPKVS
KKKLKEEKRNKSKKK

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FIGURE 54

CCCGGGAACGTGTTCTGGCTGCCGCACCCGAACAGCCTGTCCTGGTGCCCCGGCTCCCTGC
CCCGCGCCCAAGTCATGACCCTGCGCCCCCTCACTCCTCCCGCTCCATCTGCTGCTGCTGCTGC
TGCTCAGTGCGGCGGTGTGCCGGGCTGAGGCTGGGCTCGAAACCGAAAGTCCCGTCCGGACC
CTCCAAGTGGAGACCCTGGTGGAGCCCCCAGAACCATGTGCCGAGCCCGCTGCTTTTGGAGA
CACGCTTCACATACACTACACGGGAAGCTTGGTAGATGGACGTATTATTGACACCTCCCTGA
CCAGAGACCCTCTGGTTATAGAACTTGGCCAAAAGCAGGTGATTCCAGGTCTGGAGCAGAGT
CTTCTCGACATGTGTGTGGGAGAGAAGCGAAGGGCAATCATTCTTCTCACTTGGCCTATGG
AAAACGGGGATTTCCACCATCTGTCCCAGCGGATGCAGTGGTGCAGTATGACGTGGAGCTGA
TTGCACTAATCCGAGCCAACTACTGGCTAAAGCTGGTGAAGGGCATTGCTGCTGGTAGGG
ATGGCCATGGTGCCACCCTCCTGGGCCTCATTGGGTATCACCTATACAGAAAGGCCAATAGA
CCCAAAGTCTCCAAAAGAAGCTCAAGGAAGAGAAACGAAACAAGAGCAAAAAGAAATAATA
AATAATAAATTTTAAAAAACTTA

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FIGURE 55

CCGAAAGTCCCGTCCGGACCCTCCAAGTGGAGACCCTGGTGGAGCCCCAGAACCATGTGCC
GAGCCCGCTGCTTTTGGAGACACGCTTCACATACACTACACGGGAAGCTTGGTAGATGGACG
TATTATTGACACCTCCCTGACCAGAGACCCTCTGGTTATAGAACTTGGCCAAAAGCAGGTGA
TTCCAGGTCTGGAGCAGAGTCTTCTCGACATGTGTGTGGGAGAGAAGCGAAGGGCAATCATT
CCTTCTCACTTGGCCTATGGAAAACGGGGATTTCACCATCTGTCCCAGCGGATGCAGTGGT
GCAGTATGACGTGGAGCTGATTGCACTAATCCGAGCCAACTACTGGCTAAAGCTGGTGAAGG
GCATTTTGCCTCTGGTAGGGATGGCCATGGTGCCAGCCCTCCTGGGCCTCATTGGGTATCAC
CTATACAGAAAGGCCAATAGACCCAAAGTCTCCAAAAAGAAGCTCAAGGAAGAGAAACGAAA
CAAGAGCAAAAAGAAATAATAATAATAAATTTTAAAAAACTTAAAA

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FIGURE 56

CTGCTGCATCCGGGTGTCTGGAGGCTGTGGCCGTTTTGTTTTCTTGGCTAAAATCGGGGGAG
TGAGGCGGGCCGGCGCGGCGCGACACCGGGCTCCGGAACCACTGCACGACGGGGCTGGACTG
ACCTGAAAAAAATGTCTGGATTTCTAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGG
GAAAAGCGCAATACTATTGCTTCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGGTGGAT
TATCATAGATGCAGCTGTTATTTATCCCACCATGAAAGATTTCAACCACTCATACCATGCCT
GTGGTGTATAGCAACCATAGCCTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGA
GGTGATAGTTACAGTGAAGGTTGTCTGGGTCAAACAGGTGCTCGCATTGCTTTTCGTTGG
TTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTGGAGGTTATGTTG
CTAAAGAAAAAGACATAGTATACCTGGAATTGCTGTATTTTTCCAGAATGCCTTCATCTTT
TTTGGAGGGCTGGTTTTTAAGTTTGGCCGCACTGAAGACTTATGGCAGTGAACACATCTGAT
TTCCACAGCACAACAGCCCTGCATGGGTTTGTGTTTTTTTTACTGCTCACTCCCAACCTT
TTGTAATGCCATTTTCTAACTTATTTCTGAGTGTAGTCTCAGCTTAAAGTTGTGTAATACT
AAAATCACGAGAACACCTAAACAACAACCAAAAATCTATTGTGGTATGCATTGATTAACCT
ATAAAATGTTAGAGGAACTTTACATGAATAATTTTGTCAAATTTTATCATGGTATAATT
TGTA AAAATAAAAAGAAATTACAAAAGAAATTATGGATTTGTCAATGTAAGTATTGTGATA
TCTGAGGTCCAAAACCACAATGAAAGTGCTCTGAAGATTTAATGTGTTTATTCAAATGTGGT
CTCTTCTGTGTCAAATGTTAAATGAAATATAAACATTTTTTAGTTTTTAAATATTCCGTGG
TCAAATTTCTTCCTCACTATAATTGGTATTTACTTTTACCAAAAATTCTGTGAACATGTAAT
GTA ACTGGCTTTTGAGGGTCTCCAAGGGGTGAGTGGACGTGTTGGAAGAGAGAAGCACCAT
GGTCCAGCCACCAGGCTCCCTGTGTCCCTTCCATGGGAAGGTCTTCCGCTGTGCCTCTCATT
CCAAGGGCAGGAAGATGTGACTCAGCCATGACACGTGGTTCTGGTGGGATGCACAGTCACTC
CACATCCACCACTG

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FIGURE 57

MSGFLEGLRCSECIDWGEKRNTIASIAAGVLFFTGWIIIDA AVIYPTMKDFNHSYHACGVI
ATIAFLMINAVSNGQVRGDSYSEGCLGQTGARIWLFVGFMLAFGSLIASMWILFGGYVAKEK
DIVYPGIAVFFQNAFIFFGGLVFKFGRTEDLWQ

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FIGURE 58

TTCTTGGCTAAAATCGGGGGAGTGAGGCGGGCCGGCGCGGCGCGACACCGGGCTCCGGAACC
ACTGCACGACGGGGCTGGACTGACCTGAAAAAATGTCTGGATTTCTAGAGGGCTTGAGATG
CTCAGAATGCATTGACTGGGGGGAAAAGCGCAATACTATTGCTTCCATTGCTGCTGGTGTAC
TATTTTTTTACAGGCTGGTGGATTATCATAGATGCAGCTGTTATTTATCCCACCATGAAAGAT
TTCAACCACTCATACCATGCCTGTGGTGTATAGCAACCATAGCCTTCCTAATGATTAATGC
AGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTTGTCTGGGTCAAACAGGTG
CTCGCATTTGGCTTTTCGTTGGTTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGG
ATTCTTTTTTGGAGGTTATGTTGCTAAAGAAAAAGACATAGTATACCCTGGAATTGCTGTATT
TTTCCAGAATGCCTTCATCTTTTTTGGAGGGCTGGTTTTTAAGTTTGGC

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FIGURE 59

TGGACGGACCTGAAAAAATGTTTGGATTTNTAGAGGGNTTGAGATGTTTCTAGAATGCATGAC
TGGGGGAAAAGCGCAAATACTATTGCTTCCATTGCTGCTGGTGTANTATTTTTTACAGGCTG
GTGGATTATCATAGATGCAGNTGTTATTTATCCCACCATGAAAGATTTCAACCANTCATACC
ATGCCTGTGGTGTATAGCAACCATAGCCTTCNTAATGATTAATGCAGTATCGAATGGACAA
GTCCGAGGTGATAGTTACAGTGAAGGTTGTTTGGGTCAAACAGGTGCTCGCATTGCTTTT
CGTTGGTTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTGGAGGTT
ATGTTGCTAAAGAAAAAGACATAGTATACCCTGGAATTGNTGTATTTTTCCAGAATGCCTTC
ATCTTTTTTGGAGGGCTGGTTTTTAAGTTTGGCCGCACTGAAGANTTATGGCAGTG

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FIGURE 60

GGACACCGGGTTCCGGACCAATGCANGACGGGGTGGANTGACCTGAAAAAATGTTTGGATT
TTTAGAGGGCTTGAGATGNTCAGAATGCATTGACTGGGGGAAAAGCGCAATANTATTGCTTT
CCATTGCTGCTGGTGTACTATTTTTTACAGGGTGGTGGATTATCATAGATGCAGCTGTTATT
TATCCCACCATGAAAGATTTNAACCACTCATACCATGCCTGTGGTGTATAGCAACCATAGC
CTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTT
GTTTGGGTCAAACAGGTGNTCGCATTTGGCTTTTCGTTGGTTTCATGTTGGCCTTTGGATTT
CTGATTGNATTCTATGCGGATTCTTCTTGGAGGTTATGTTGCTAAAGAAAAAGACATAGTAT
ACCCTGGAATTNCTNTATTTTTCCAGAATGCC

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FIGURE 61

TAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGGGAAAAGCGCAATANTATTGCTTCC
ATTGNTGNTGGTGTANTATTTTTTTTACAGGCTGGTGGATTATNATAGATGCAGCTGTTATTT
ATCCCACCATGAAAGATTTNAACCANTCATACCATGCCTGTGGTGTATAGCAACCATAGCC
TTCCTAATGATTAATGCAGTATNGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTTG
TTTGGGTCAAACAGGTGNTNGCATTGCTTTTNGTTGGTTTCATGTTGGCCTTTGGATCTN
TGATTGCATTTATGTGGATTNTTTTTTGGAGGTTATGTTGCTAAAGNAAAAGACATAGTATAC
CCTGT

FIGURE 62

GGGAGGCTGTGNCCGTTTTGTTTTNTTGGCTAAAATCGGGGGAGTGAGGCGGCCCCGGCGCGG
CGNGACACCGGGTTCCGGGAACCATTCACGACGGGGTGGACTGACCTGAAAAAATGTTTG
GATTTNTAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGGGAAAAGCGCAATACTATT
GCTTCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGGTGGATTATCATAGATGCAGCTGT
TATTTATCCCACCATGAAAGATTTCAACCACTCATACCATGCCTGTGGTGTATAGCAACCA
TAGCCTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAA
GGTTGTCTGGGTCAAACAGGTGCTCGCATTTGGCTTTTCGTTGGTTTCATGTTGGCCTTTGG
ATNTCTGATTGCATCTATGTGGATTCTTTTTGGAGGTTATGTTGCTAAAGAAAAAGACATAG
TATACCCTGGAATTGCTGTATTTTTCCAGAATGCCTTCATNTTTTTTGGAGGGCTG

FIGURE 63

CGACGCCGGCGTGATGTGGCTTCCGCTGGTGCTGCTCCTGGCTGTGCTGCTGCTGGCCGTCCTCTGCAAAGTTTACTTGGGACTATTCTCTGGCAGCTCCCCGAATCCTTTCTCCGAAGATGTC
AAACGGCCCCCAGCGCCCCCTGGTAAGTACGAGGAGGCCAGGAAGAAGGTTCTCAAACAAGC
TTTTTTCAGCCAACCAAGTGCCGGAGAAGCTGGATGTGGTGGTAATTGGCAGTGGCTTTGGGG
GCCTGGCTGCAGCTGCAATTCTAGCTAAAGCTGGCAAGCGAGTCCTGGTGTGGAACAACAT
ACCAAGGCAGGGGGCTGCTGTACATACCTTTGGAAAGAATGGCCTTGAATTTGACACAGGAAT
CCATTACATTGGGCGTATGGAAGAGGGCAGCATTGGCCGTTTATCTTGGACCAGATCACTG
AAGGGCAGCTGGACTGGGCTCCCTGTCTCTCTTTTGACATCATGGTACTGGAAGGGCCC
AATGGCCGAAAGGAGTACCCCATGTACAGTGGAGAGAAAGCCTACATTACAGGGCCTCAAGGA
GAAGTTTCCACAGGAGGAAGCTATCATTTGACAAGTATATAAAGCTGGTTAAGGTGGTATCCA
GTGGAGCCCCCTCATGCCATCCTGTTGAAATTCCTCCCATTTGCCGTGGTTCAGTCTCTCGAG
AGGTGTGGGCTGCTGACTCGTTTCTCTCCATTCTTCAAGCATCCACCCAGAGCCTGGGTGA
GGTCCTGCAGCAGCTGGGGGCCCTCTCTGAGCTCCAGGCAGTACTCAGCTACATCTTCCCCA
CTTACGGTGTACCCCCAACCACAGTGCCTTTTCCATGCACGCCCTGCTGGTCAACCACTAC
ATGAAAGGAGGCTTTTATCCCCGAGGGGGTTCAGTGAAATTGCCTTCCACACCATCCCTGT
GATTCAGCGGGCTGGGGGCGCTGTCTCACAAGGCCACTGTGCAGAGTGTGTTGCTGGACT
CAGCTGGGAAAGCCTGTGGTGTGAGTGTGAAGAAGGGGCATGAGCTGGTGAACATCTATTGC
CCCATCGTGGTCTCCAACGCAGGACTGTTCAACACCTATGAACACCTACTGCCGGGGAACGC
CCGCTGCCTGCCAGGTGTGAAGCAGCAACTGGGGACGGTGCAGCCCGGCTTAGGCATGACCT
CTGTTTTTCTGCTGCGAGGCACCAAGGAAGACCTGCATCTGCCGTCCACCACTACTAT
GTTTACTATGACACGGACATGGACAGGCGATGGAGCGCTACGTCTCCATGCCAGGGAAGA
GGCTGCGGAACACATCCCTCTTCTCTTCTCGCTTTCCCATCAGCCAAAGATCCGACCTGGG
AGGACCGATTCCCAGGCCGGTCCACCATGATCATGCTCATACCCACTGCCTACGAGTGGTTT
GAGGAGTGGCAGGCGGAGCTGAAGGGAAAGCGGGCAGTGACTATGAGACCTTCAAAAACTC
CTTTGTGGAAGCCTCTATGTGAGTGGTCTGAAACTGTTCCCACAGCTGGAGGGGAAGGTGG
AGAGTGTGACTGCAGGATCCCCACTCACCAACCAGTTCTATCTGGCTGCTCCCCGAGGTGCC
TGCTACGGGGCTGACCATGACCTGGGCGCCTGCACCCTTGTGTGATGGCTCCTTGAGGGC
CCAGAGCCCCATCCCCAACCTCTATCTGACAGGCCAGGATATCTTACCTGTGGACTGGTCG
GGGCCCTGCAAGGTGCCCTGCTGTGCAGCAGCGCCATCCTGAAGCGGAAGTTGTACTCAGAC
CTTAAGAATCTTGATTCTAGGATCCGGGCACAGAAGAAAAAGAATTAGTTCCATCAGGGAGG
AGTCAGAGGAATTTGCCCAATGGCTGGGGCATCTCCCTTGACTTACCCATAATGTCTTTCTG
CATTAGTTCTTGCACGTATAAAGCACTCTAATTTGGTTCTGATGCCTGAAGAGAGGCCTAG
TTTAAATCACAATCCGAATCTGGGGCAATGGAATCACTGCTTCCAGCTGGGGCAGGTGAGA
TCTTTACGCCTTTTATAACATGCCATCCCTACTAATAGGATATTGACTTGGATAGCTTGATG
TCTCATGACGAGCGGCGCTCTGCATCCCTCACCCATGCCTCCTAACTCAGTGATCAAAGCGA
ATATTCCATCTGTGGATAGAACCCTGGCAGTGTGTGTCAGCTCAACCTGGTGGGTTGAGTTC
TGTCCTGAGGCTTCTGCTCTCATTTAGTGCTACGCTGCACAGTTCTACACTGTCAAGG
GAAAAGGGAGACTAATGAGGCTTAACCTCAAAACCTGGGCGTGGTTTTGGTTGCCATTCCATA
GGTTTGGAGAGCTCTAGATCTCTTTTGTGCTGGGTTGAGTGGCTCTTCAGGGGACAGGAAAT
GCCTGTGTCTGGCCAGTGTGGTCTGAGGCTTTGGGGTAACAGCAGGATCCATCAGTTAGTA
GGGTGCATGTGAGATGATCATATCCAATTCATATGGAAGTCCGGGGTCTGTCTTCTTATCA
TCGGGGTGGCAGCTGGTCTCAATGTGCCAGCAGGGACTCAGTACCTGAGCCTCAATCAAGC
CTTATCCACCAAATACACAGGGAAGGGTGATGCAGGGAAGGGTGACATCAGGAGTCAGGGCA
TGGACTGGTAAGATGAATACTTTGCTGGGCTGAAGCAGGCTGCAGGGCATTCAGCCAAAGGG
CACAGCAGGGGACAGTGCAGGGAGGTGTGGGGTAAGGGAGGGAAGTCACATCAGAAAAGGGA
AAGCCACGGAATGTGTGTGAAGCCCAGAAATGGCATTGTCAGTTAATTAGCACATGTGAGGG
TTAGACAGGTAGGTGAATGCAAGCTCAAGGTTTGGAAAAATGACTTTTCACTTATGTCTTTG
GTATCAGACATACGAAAGGTCTCTTTGTAGTTTCGTGTTAATGTAACATTAATAAATTTATTG
ATTCCATTGCTTTAAAAA

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FIGURE 64

MWLPLVLLLAVLLLAVLCKVYLGLFSGSSPNPFSEDVKRPPAPLVTDKEARKKVLKQAFSAN
QVPEKLDVVVIGSGFGGLAAAAILAKAGKRVLVLEQHTKAGGCCHTFGKNGLEFDTGIHYIG
RMEEGSIGRFILDQITEGQLDWAPLSSPFDIMVLEGPNGRKEYPMYSGEKAYIQGLKEKFPQ
EEAIIIDKYIKLVKVSSGAPHAILLKFLPLPVVQLLDRCGLLTRFSPFLQASTQSLAEVLQQ
LGASSELQAVLSYIFPTYGVTPNHSAFSMHALLVNHYMKGGFYPRGGSSEIAFHTIPVIQRA
GGAVLTKATVQSVLLDSAGKACGVSVKKGHELVNIYCPIVVSNAGLFNTYEHLLPGNARCLP
GVKQQLGTVRPGLGMTSVFICLRGTKEDLHLPSTNYYVYYDTMDQAMERYVSMFREEAAEH
IPLFFAFPSAKDPTWEDRFPGRSTMIMLIPTAYEWFEWQAELKGKRGSDYETFKNSFVEA
SMSVVLKLFQLEGKVESVTAGSPLTNQFYLAAPRGACYGADHDLGRLHPCVMASLRAQSPI
PNLYLTGQDIFTCGLVGALQGALLCSSAILKRNLVSDLKNLDSRIRAQKKKN

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FIGURE 65

GCAGCGGCGAGGCGGCGGTGGTGGCTGAGTCCGTGGTGGCAGAGGCGAAGGCGACAGCTCTA
GGGGTTGGCACCGGCCCGAGAGGAGGATGCGGGTCCGGATAGGGCTGACGCTGCTGCTGTG
TGCGGTGCTGCTGAGCTTGGCCTCGGCGTCCTCGGATGAAGAAGGCAGCCAGGATGAATCCT
TAGATTCCAAGACTACTTTGACATCAGATGAGTCAGTAAAGGACCATACTACTGCAGGCAGA
GTAGTTGCTGGTCAAATATTTCTTGATTGAGAAGAATCTGAATTAGAATCCTCTATTCAAGA
AGAGGAAGACAGCCTCAAGAGCCAAGAGGGGGAAAGTGTACAGAAGATATCAGCTTTCTAG
AGTCTCCAAATCCAGAAAACAAGGACTATGAAGAGCCAAAGAAAGTACGGAAACCAGCTTTG
ACCGCCATTGAAGGCACAGCACATGGGGAGCCCTGCCACTTCCCTTTTCTTTTCCTAGATAA
GGAGTATGATGAATGTACATCAGATGGGAGGGAAGATGGCAGACTGTGGTGTGCTACAACCT
ATGACTACAAAGCAGATGAAAAGTGGGGCTTTTGTGAACTGAAGAAGAGGCTGCTAAGAGA
CGGCAGATGCAGGAAGCAGAAATGATGTATCAAACCTGGAATGAAAATCCTTAATGGAAGCAA
TAAGAAAAGCCAAAAAAGAGAAGCATATCGGTATCTCCAAAAGGCAGCAAGCATGAACCATA
CCAAAGCCCTGGAGAGAGTGTATATGCTCTTTTATTTGGTGATTACTTGCCACAGAATATC
CAGGCAGCGAGAGAGATGTTTGAGAAGCTGACTGAGGAAGGCTCTCCCAAGGGACAGACTGC
TCTTGCTTTTCTGTATGCCTCTGGACTTGGTGTTAATTCAAGTCAGGCCAAAGGCTCTTGAT
ATTATACATTTGGAGCTCTTGGGGCAATCTAATAGCCCACATGGTTTTGGTAAGTAGACTT
TAGTGGAAGGCTAATAATATTAACATCAGAAGAATTTGTGGTTTATAGCGGCCACAACTTTT
TCAGCTTTCATGATCCAGATTTGCTTGTATTAAGACCAAATATTCAGTTGAACTTCCTTCAA
ATTCTTGTTAATGGATATAACACATGGAATCTACATGTAAATGAAAGTTGGTGGAGTCCACA
ATTTTTCTTTAAATGATTAGTTTGGCTGATTGCCCTAAAAAGAGAGATCTGATAAATGGC
TCTTTTAAATTTTCTCTGAGTTGGAATTGTCAGAATCATTTTTTACATTAGATTATCATAA
TTTTAAAAATTTTCTTTAGTTTTTCAAATTTTGTAAATGGTGGCTATAGAAAAACAACAT
GAAATATTATACAATATTTTGCAACAATGCCCTAAGAATTGTTAAATTCATGGAGTTATTT
GTGCAGAATGACTCCAGAGAGCTCTACTTTCTGTTTTTTACTTTTCATGATTGGCTGTCTTC
CCATTTATTCTGGTCATTTATTGCTAGTGACACTGTGCCTGCTTCCAGTAGTCTCATTTTCC
CTATTTTGCTAATTTGTTACTTTTTCTTTGCTAATTTGGAAGATTAACTCATTTTTTAATAAA
ATTATGTCTAAGATTAAA
AAA

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FIGURE 66

MRVRIGLTLLLCVLLSLASASSDEEGSQDESLSKTTLTSDSVKDHTTAGRVVAGQIFLD
SESELESSIQEEEDSLKSQEGESVTEDISFLESPNPENKDYEEPKKVRKPALTAIEGTAHG
EPCHFPPFLFLDKEYDECTSDGREDGRLWCATTYDYKADEKWGFCETEEEEAAKRRQMQAEMM
YQTGMKILNGSNKKSQKREAYRYLQKAASMNHTKALERVSYALLFGDYLPQNIQAAREMF EK
LTEEGSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLI AHMVLVSRL

FIGURE 67

CTTCCCAGCCCTGTGCCCCAAAGCACCTGGAGCATATAGCCTTGCAGAACTTCTACTTGCCT
GCCTCCCTGCCTCTGGCCATGGCCTGCCGGTGCCTCAGCTTCCTTCTGATGGGGACCTTCCT
GTCAGTTTCCCAGACAGTCCTGGCCCAGCTGGATGCACTGCTGGTCTTCCCAGGCCAAGTGG
CTCAACTCTCCTGCACGCTCAGCCCCCAGCACGTCACCATCAGGGACTACGGTGTGTCCTGG
TACCAGCAGCGGGCAGGCAGTGCCCCTCGATATCTCCTCTACTACCGCTCGGAGGAGGATCA
CCACCGGCCTGCTGACATCCCCGATCGATTCTCGGCAGCCAAGGATGAGGCCCACAATGCCT
GTGTCCTCACCATTAGTCCCGTGCAGCCTGAAGACGACGCGGATTACTACTGCTCTGTTGGC
TACGGCTTTAGTCCCTTAGGGGTGGGGTGTGAGATGGGTGCCTCCCCCTCTGCCTCCCATTTCT
GCCCCTGACCTTGGGTCCCTTTTAAACTTTCTCTGAGCCTTGCTTCCCCTCTGTAAAATGGG
TTAATAATATTCAACATGTCAACAAC

FIGURE 68

MACRCLSFLLMGTFLSVSQTVLAQLDALLVFPGQVAQLSCTLSPQHVTIRDYGVSWYQQRAG
SAPRYLLYYRSEEDHHRPADIPDRFSAKDEAHNACVLTISPVPEDDADYYCSVGYGFSF.

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FIGURE 69

GCCGCCCCGCCCCGAGACCGGGCCCCGGGGCGCGGGGCGGCGGGATGCGGCGCCCGGGGCGG
CGATGACCGCGGAGCGCACGCCGCGGGCCCCGGCCCTGACCCCGCCGCCCCGCTGAGCCC
CCCCGCGAGGTCCGGACAGGCCGAGATGACGCCGAGCCCCCTGTTGCTGCTCCTGCTGCCGC
CGCTGCTGCTGGGGGCCCTTCCCACCGGCCCGCCGCCCCGAGGCCCCCAAAGATGGCGGAC
AAGGTGGTCCCACGGCAGGTGGCCCCGGCTGGGCCGCACTGTGCGGCTGCAGTGCCAGTGGA
GGGGGACCCGCCGCGCTGACCATGTGGACCAAGGATGGCCGCACCATCCACAGCGGCTGGA
GCCGCTTCCGCGTGCTGCCGCAGGGGCTGAAGGTGAAGCAGGTGGAGCGGGAGGATGCCGGC
GTGTACGTGTGCAAGGCCACCAACGGCTTCGGCAGCCTGAGCGTCAACTACACCCTCGTCGT
GCTGGATGACATTAGCCCAGGGAAGGAGAGCCTGGGGCCCCGACAGCTCCTCTGGGGGTCAAG
AGGACCCCGCCAGCCAGCAGTGGGCACGACCGCGCTTCACACAGCCCTCCAAGATGAGGCGC
CGGGTGATCGCACGGCCCCGTGGGTAGCTCCGTGCGGCTCAAGTGCGTGCCAGCGGGCACCC
TCGGCCCCGACATCACGTGGATGAAGGACGACCAGGCCTTGACGCGCCGAGAGGCCGCTGAGC
CCAGGAAGAAGAAGTGGACACTGAGCCTGAAGAACCTGCGGCCGGAGGACAGCGGCAAATAC
ACCTGCCGCGTGTCGAACCGCGCGGGCGCCATCAACGCCACCTACAAGGTGGATGTGATCCA
GCGGACCCGTTCCAAGCCCCGTGCTCACAGGCACGCACCCCGTGAACACGACGGTGGACTTCG
GGGGGACCACGTCTTCCAGTGCAAGGTGCGCAGCGACGTGAAGCCGGTGATCCAGTGGCTG
AAGCGCGTGGAGTACGGCGCCGAGGGCCGCCACAACTCCACCATCGATGTGGGCGGCCAGAA
GTTTGTGGTGCTGCCACGGGTGACGTGTGGTTCGGGCCCGACGGCTCCTACCTCAATAAGC
TGCTCATCACCCGTGCCCGCCAGGACGATGCGGGCATGTACATCTGCCTTGGCGCCAAACAC
ATGGGCTACAGCTTCCGCAGCGCCTTCTCACCGTGCTGCCAGACCCAAAACCGCCAGGGCC
ACCTGTGGCCTCCTCGTCCTCGGCCACTAGCCTGCCGTGGCCCGTGGTCATCGGCATCCCAG
CCGGCGCTGTCTTCATCCTGGGCACCCTGCTCCTGTGGCTTTGCCAGGCCCAGAAGAAGCCG
TGCACCCCCGCGCCTGCCCTCCCCCTGCCCTGGGCACCGCCCCGCGGGGACGGCCCGCGACCG
CAGCGGAGACAAGGACCTTCCCTCGTTGGCCGCCCTCAGCGCTGGCCCTGGTGTGGGGCTGT
GTGAGGAGCATGGGTCTCCGGCAGCCCCCAGCACTTACTGGGCCAGGCCAGTTGCTGGC
CCTAAGTTGTACCCCAAACCTCTACACAGACATCCACACACACACACACACTCTCACAC
ACACTCACACGTGGAGGGCAAGGTCCACCAGCACATCCACTATCAGTGCTAGACGGCACCGT
ATCTGCAGTGGGCACGGGGGGGCGGCCAGACAGGCAGACTGGGAGGATGGAGGACGGAGCT
GCAGACGAAGGCAGGGGACCCATGGCGAGGAGGAATGGCCAGCACCCAGGCAGTCTGTGTG
TGAGGCATAGCCCCTGGACACACACACACAGACACACACACTACCTGGATGCATGTATGCAC
ACACATGCGCGCACACGTGCTCCCTGAAGGCACACGTACGCACACGCACATGCACAGATATG
CCGCTGGGCACACAGATAAGCTGCCCAAATGCACGCACACGCACAGAGACATGCCAGAACA
TACAAGGACATGCTGCCTGAACATAACACGCACACCCATGCGCAGATGTGCTGCCTGGACA
CACACACACACAGGATATGCTGTCTGGACGCACACACGTGCAGATATGGTATCCGGACACA
CACGTGCACAGATATGCTGCCTGGACACACAGATAATGCTGCCTTGACACACATGCACGG
ATATTGCCTGGACACACACACACACACACGCGTGCACAGATATGCTGTCTGGACACGCACAC
ACATGCAGATATGCTGCCTGGACACACACTTCCAGACACACGTGCACAGGCGCAGATATGCT
GCCTGGACACACGCAGATATGCTGTCTAGTCACACACACACGCAGACATGCTGTCCGGACAC
ACACACGCATGCACAGATATGCTGTCCGGACACACACACGCACGCAGATATGCTGCCTGGAC
ACACACACAGATAATGCTGCCTCAACACTCACACACGTGCAGATATTGCCTGGACACACACA
TGTGCACAGATATGCTGTCTGGACATGCACACACGTGCAGATATGCTGTCCGGATACACACG
CACGCACACATGCAGATATGCTGCCTGGGCACACACTTCCGGACACACATGCACACACAGGT
GCAGATATGCTGCCTGGACACACACACAGATAATGCTGCCTCAACACTCACACACGTGCAGA
TATTGCCTGGACACACACATGTGCACAGATATGCTGTCTGGACATGCACACACGTGCAGATA
TGCTGTCCGGATACACACGCACGCACACATGCAGATATGCTGCCTGGGCACACACTTCCGGA
CACACATGCACACACAGGTGCAGATATGCTGCCTGGACACACGCAGACTGACGTGCTTTTGG
GAGGGTGTGCCGTGAAGCCTGCAGTACGTGTGCCGTGAGGCTCATAGTTGATGAGGGACTTT
CCCTGCTCCACCGTCACTCCCCAACTCTGCCCGCCTCTGTCCCCGCCTCAGTCCCCGCCTC
CATCCCCCCTCTGTCCCCTGGCCTTGGCGGCTATTTTTGCCACCTGCCTTGGGTGCCCAGG
AGTCCCCCTGCTGTGGGCTGGGGTTGGGGGCACAGCAGCCCCAAGCCTGAGAGGCTGGAG
CCCATGGCTAGTGGCTCATCCCCAGTGCACTTCTCCCCCTGACACAGAGAAGGGGCCTTGGTA
TTTATATTTAAGAAATGAAGATAATATTAATAATGATGGAAGGAAGACTGGGTGTCAGGGAC
TGTGGTCTCTCCTGGGGCCCCGGGACCCGCTGGTCTTTCAGCCATGCTGATGACCACACCCC
GTCCAGGCCAGACACCACCCCCACCCACTGTCTGTTGGTGGCCCCAGATCTCTGTAATTTTA
TGTAGAGTTTGAGCTGAAGCCCCGTATATTTAATTTATTTTGTAAACACAAAA

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FIGURE 70

MTPSPLLLLLLPPLLLGAFPPAAAARGPPKMADKVVPRQVARLGRTVRLQCPVEGDPPPLTM
WTKDGRTIHSGWSRFRVLPQGLKVKQVEREDAGVYVCKATNGFGSLSVNYTLVVLDDISPGK
ESLGPDSSSGGQEDPASQQWARPRFTQPSKMRRRVIAIPVGSSVRLKCVASGHPRPDITWMK
DDQALTRPEAAEPRKKKWTLSLKNLRPEDSGKYTCRVSNRAGAINATYKVDVIQRTRSKPVL
TGTHPVNTTVDFGGTTSFQCKVRSDVKPVIQWLKRVEYGAEGRHNSTIDVGGQKFVVLPTGD
VWSRPDGSYLNKLLITRARQDDAGMYICLGANTMGYSFRSAFLTIVLPDPKPPGPPVASSSSA
TSLPWPVVIGIPAGAVFILGTLLLWLCQAQKKPCTPAPAPPLPGHRPPGTARDRSGDKDLPS
LAALSAGPGVGLCEEHGSPAAPQHLLGPGPVAGPKLYPKLYTDIHTHTHTSHHTSHVEGKV
HQHIHYQC

FIGURE 71A

CCCAGCTGAGGAGCCCTGCTCAAGACACGGTCACTGGATCTGAGAACTTCCCAGGGGACCG
CATTCCAGAGTCAGTGA CTCTGTGAAGCACCCACATCTACCTCTTGCCACGTTCCCACGGGC
TTGGGGGAAAGATGGTGGGGACCAAGGCCTGGGTGTTCTCCTTCTGGTCTGGAAGTCACA
TCTGTGTTGGGGAGACAGACGATGCTCACCCAGTCAGTAAGAAGAGTCCAGCCTGGGAAGAA
GAACCCAGCATCTTTGCCAAGCCTGCCGACACCCTGGAGAGCCCTGGTGAAGTGGACAACAT
GGTTCAACATCGACTACCCAGGCGGGAAGGGCGACTATGAGCGGCTGGACGCCATTGCTTC
TACTATGGGGACCGTGTATGTGCCCGTCCCCTGCGGCTAGAGGCTCGGACCACTGACTGGAC
ACCTGCGGGCAGCACTGGCCAGGTGGTCCATGGTAGTCCCCGTGAGGGTTTCTGGTGCCTCA
ACAGGGAGCAGCGGCCTGGCCAGAACTGCTCTAATTACACCGTACGCTTCTCTGCCCCACCA
GGATCCCTGCGCCGAGACACAGAGCGCATCTGGAGCCCATGGTCTCCCTGGAGCAAGTGCTC
AGCTGCCTGTGGTCAGACTGGGGTCCAGACTCGCACACGCATTTGCTTGGCAGAGATGGTGT
CGCTGTGCAGTGAGGCCAGCGAAGAGGGTCAGCACTGCATGGGCCAGGACTGTACAGCCTGT
GACCTGACCTGCCCAATGGGCCAGGTGAATGCTGACTGTGATGCCTGCATGTGCCAGGACTT
CATGCTTCATGGGGCTGTCTCCCTTCCCGAGGTGCCCCAGCCTCAGGGGCTGCTATCTACC
TCCTGACCAAGACGCCGAAGCTGCTGACCCAGACAGACAGTGATGGGAGATTCCGAATCCCT
GGCTTGTGCCCTGATGGCAAAGCATCCTGAAGATCACAAAGGTCAAGTTTGGCCCCATTGT
ACTCACAATGCCAAGACTAGCCTGAAGGCAGCCACCATCAAGGCAGAGTTTGTGAGGGCAG
AGATCCATATGCTGATGAACCTGAGACAAAAGCACGGAGAGCTGGGCAGAGCTGTCT
CTGTGCTGTAAGGCCACAGGGAAGCCAGGCCAGACAAGTATTTTGGTATCATATGACAC
ATTGCTGGATCCTTCCCTCTACAAGCATGAGAGCAAGCTGGTGTGAGGAACTGCAGCAGC
ACCAGGCTGGGGAGTACTTTTGAAGGCCAGAGTGATGCTGGGGCTGTGAAGTCCAAGGTT
GCCAGCTGATTGTACAGCATCTGATGAGACTCCTTGCAACCCAGTTCTGAGAGCTATCT
TATCCGGCTGCCCCATGATTGCTTTTCAAGATGCCACCAACTCCTTCTACTATGACGTGGGAC
GCTGCCCTGTAAAGACTTGTGCAGGGCAGCAGGATAATGGGATCAGGTGCCGTGATGCTGTG
CAGAACTGCTGTGGCATCTCCAAGACAGAGGAAGGGAGATCCAGTGCAAGTGGCTACACGCT
ACCCACCAAGGTGGCCAAGGAGTGCACTGCCAGCGGTGTACGGAACCTCGGAGCATCGTGC
GGGGCCGTGTCACTGCTGCTGACAATGGGGAGCCCATGCGCTTTGGCCATGTGTACATGGGG
AACAGCCGTGTAAGCATGACTGGCTACAAGGGCACTTTTCAACCTCCATGTCCCCCAGGACAC
TGAGAGGCTGGTGCTCACATTTGTGGACAGGCTGCAGAAAGTTTGTCAACACCACCAAGTGC
TACCTTTCAACAAGAAGGGGAGTGCCGTGTTCCATGAAATCAAGATGCTTCGTGCGAAAGAG
CCCATCACTTTTGAAGCCATGGAGACCAACATCATCCCCCTGGGGGAAGTGGTTGGTGAAGA
CCCCATGGCTGAACTGGAGATTCCATCCAGGAGTTTCTACAGGCAGAATGGGGAGCCCTACA
TAGGAAAGTGAAGGCCAGTGTGACCTTCTGGATCCCCGGAATATTTCCACAGCCACAGCT
GCCAGACTGACCTGAACTTCATCAATGACGAAGGAGACACTTTTCCCCCTTCGGACGTATGG
CATGTTCTCTGTGGA CTTCAGAGATGAGGTACCTCAGAGCCACTTAATGCTGGCAAAGTGA
AGGTCCACCTTGACTCGACCCAGGTCAAGATGCCAGAGCACATATCCACAGTGAACTCTGG
TCACTCAATCCAGACACAGGGCTGTGGGAGGAGGAAGGTGATTTCAAATTTGAAAATCAAAG
GAGGAACAAAAGAGAAGACAGAACCTTCTGGTGGGCAACCTGGAGATTCTGTGAGAGGAGGC
TCTTTAACCTGGATGTTCTGAAAGCAGGCGGTGCTTTGTTAAGGTGAGGGCTACCGGAGT
GAGAGGTTCTTGCCTAGTGAGCAGATCCAGGGGGTGTGATCTCCGTGATTAACTGGAGCC
TAGAATGCTGCTTCTTGTCCAACCTAGGCTGGGGCCGCTTTGACAGTGTCTACAGGCC
CCAACGGGGCCTGTGTGCCTTCTGTGATGACCACTCCCTGATGCCTACTCTGCCTAT
GTCTTGGCAAGCCTGGCTGGGGAGGAACTGCAAGCAGTGGAGTCTTCTCCTAAATTCAACCC
AAATGCAATTGGCGTCCCTCAGCCCTATCTCAACAAGCTCAACTACCGTCGGACGGACCATG
AGGATCCACGGGTAAAAAGACAGCTTCCAGATTAGCATGGCCAAGCCAAGGCCCAACTCA
GCTGAGGAGAGCAATGGGCCCATCTATGCCTTTGAGAACCTCCGGGCATGTGAAGAGGCACC
ACCCAGTGACGCCACTTCCGGTTCTACCAGATTGAGGGGGATCGATATGACTACAACACAG
TCCCCTTCAACGAAGATGACCCTATGAGCTGGACTGAAGACTATCTGGCATGGTGGCCAAAG
CCGATGGAATTCAGGGCCTGCTATATCAAGGTGAAGATTGTGGGGCACTGGAAGTGAATGT
GCGATCCCGCAACATGGGGGGCACTCATCGGCGGACAGTGGGGAAGCTGTGTAATCCGAG
ATGTGAGGAGCACTCGGGACAGGGACCAAGCCATGTCTCAGCTGCCTGTCTGGAGTTCAAG
TGCAGTGGGATGCTCTATGATCAGGACCGTGTGGACCGCACCTGGTGAAGGTCATCCCCCA
GGGCAGCTGCCGTGAGCCAGTGTGAACCCCATGCTGCATGAGTACCTGGTCAACCACTTGC
CACTTGCACTCAACAACGACACCAAGTGAAGTACACCATGCTGGCACCTTGGACCCACTGGGC
CACAATATGGCATCTACACTGTCACTGACCAGGACCCTCGCACGGCCAAGGAGATCGCGCT
CGGCCGGTGTCTTGTATGGCACATCCGATGGCTCCTCCAGAATCATGAAGAGCAATGTGGGAG
TAGCCCTCACCTTCAACTGTGTAGAGAGGCAAGTAGGCCCGCAGAGTGCCTTCCAGTACCTC
CAAAGCACCCAGCCAGTCCCCTGCTGAGGCACTGTCCAAGGAAGAGTGCCTTCAGGGAG
GCAGCAGCGAGCGAGCAGGGGTGGCCAGCGCCAGGGTGGAGTGGTGGCCTCTCTGAGATTTCT

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FIGURE 71B

CTAGAGTTGCTCAACAGCCCCTGATCAACTTAAGTTTTGTGGTACTTCACCCTCTTCTGCCCT
CATTTTCATGTGACAGCCATTGTGAGACTGATGCACAACTGTCACCTGGTTAATTTAAGCAC
TTCTGTTTTCGTGAATTTGCTTGTTTGTTCCTTCATGCCTTTACTTACTTTGTCCCATGCTA
CTGATTGGCACGTGGCCCCCACAATGGCACAATAAAGCCCCTTTGTGAACTGTTCTTTAAA
TGAAACACAAGAAATTGGCCACTGGTAAACTCTGCAGCTTCAACTGTACTTCATTTAATGC
CATTAATGCAAATATACTTCCTCTTCTTTTTGCATGGTTTTGCCACCTCTGCAATAGTGAT
AATCTGATGCTGAAGATCAAATAACCAATATAAAGCATATTTCTTGGCCTTGCTCCACAGGA
CATAGGCAAGCCTTGATCATAGTTCATACATATAAATGGTGGTGAAATAAAGAAATAAAACA
CAATACTTTTACTTGAAATGTAAATAACTTATTTATTTCTTTGCTAAATTTGGAATTCTAGT
GCACATTCAAAGTTAAGCTATTAAATATAGGGTGATCATAGTTCCTCTACCAAGTCTGGAAA
GAACATCTCCTGGTATCCACAATTACACCAGGTTGCTAACTGTATTTGTACATTTCCCTTTG
CATTCGCTTTTGTCTTGCTAGAAACCCAGTGTAGCCCAGGGCAGATGTCAATAAATGCATA
CTCTGTATTTTGAAAAAA

FIGURE 72

MVGTKAWVFSFLVLEVTSVLGRQTM LTQSVRRVQPGKKNPSIFAKPADTLESPGEWTTWFNI
DYPGGKGDYERLDAIRFYYGDRVCARPLRLEARTTDWTPAGSTGQVVHGSPREGFWCLNREQ
RPGQNC SNYTVRFLCPPGSLRRDTERIWSPWSPWSKCSAACGQTGVQTRTRICLAEMVSLCS
EASEEGQHCMGQDCTACDLTCPMGQVNADCDACMCQDFMLHGAVSLPGGAPASGAAIYLLTK
TPKLLTQTDS DGRFRI PGLCPDGKSILKITKVKFAPIVLTMPKTS LKAATIKA EFVRAETPY
MVMNPETKARRAGQSVSLCCKATGKPRPDKYFWYHNDTLLDPSLYKHESKLVLRLK LQQHQAG
EYFCKAQSDAGAVKSKVAQLIVTASDETPCNPVPESYLIRLPHDCFQ NATNSFY YDVGRCPV
KTCAGQQDNGIRCRDAVQNC CGISKTEEREIQCSGYTLPTKVAKECSCQRCTETRSIVRGRV
SAADNGEPMRFGHVYMGNSRVSM TGYKGTFTLHVPQDTERLVLT FVDRLQKFVNTTKVL PFN
KKGS AVFHEIKMLRRKEPIT LEAMETNIIPLGEVVGEDPMAELEIPSR SFYRQNGEPYIGKV
KASVTFLDPRNISTATAAQTD LNFINDEGDTFPLRTYGMFSVD FRDEVTSEPLNAGKV KVHL
DSTQVKMPEHISTVKLWSLNPDTGLWEEEGDFKFENQRRNKREDRTFLVGNLEIRERRLFNL
DVPESRRCFVKVRAYRSE RFLPSEIQGVVISVINLEPRTGFLSNPRAWGRFDSVITGPNGA
CVPAPCDDQSPDAYSAYVLASLAGEELQAVESSPKFNPNAIGVPQPYLNKLN YRRTDHEDPR
VKKTAFQISMAKPRPNSAEESNGPIYAFENLRACEEAPPSAAHFRFYQIEGDRYDYNTVPFN
EDDPMSWTE DYLA WPKPMEFRACYIKVKIVGPLEVNVR SRNMGGTHRRTVGKLYGIRDVRS
TRDRDQPNVSAACLEFKCSGMLYDQDRVDRTL VKVIPQGSCRRASVNPM LHEYLVNHLPLAV
NNDTSEYTMLAPLDPLGHNYGIYTVTDQDPRTAKEIALGRCFDGTSDGSSRIMKSNVGVALT
FNCVERQVGRQSAFQYLQSTPAQSPAAGTVQGRVPSRRQQRASRGGQRQGGVVASLRFP RVA
QQPLIN

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FIGURE 73

CTGCAAGTTGTTAAACGCCTAACACACAAGTATGTTAGGCTTCCACCAAAGTCCTCAATATAC
CTGAATACGCACAATATCTTAACTCTTCATATTTGGTTTGGGATCTGCTTTGAGGTCCCAT
CTTCATTTAAAAAAAATACAGAGACCTACCTACCCGTACGCATACATACATATGTGTATAT
ATATGTAAACTAGACAAAGATCGCAGATCATAAAGCAAGCTCTGCTTTAGTTTCCAAGAAGA
TTACAAAGAATTTAGAGATGTATTTGTCAAGATCCCTGTGCGATTTCATGCCCTTTGGGTTACG
GTGTCCTCAGTGATGCAGCCCTACCCTTTGGTTTGGGGACATTATGATTTGTGTAAGACTCA
GATTTACACGGAAGAAGGGAAAGTTTGGGATTACATGGCCTGCCAGCCGGAATCCACGGACA
TGACAAAATATCTGAAAGTGAACTCGATCCTCCGGATATTACCTGTGGAGACCCTCCTGAG
ACGTTCTGTGCAATGGGCAATCCCTACATGTGCAATAATGAGTGTGATGCGAGTACCCCTGA
GCTGGCACACCCCCCTGAGCTGATGTTTGATTTTGAAGGAAGACATCCCTCCACATTTTGGC
AGTCTGCCACTTGGAAGGAGTATCCCAAGCCTCTCCAGGTTAACATCACTCTGTCTTGAGC
AAAACCATTGAGCTAACAGACAACATAGTTATTACCTTTGAATCTGGGCGTCCAGACCAAAT
GATCCTGGAGAAGTCTCTCGATTATGGACGAACATGGCAGCCCTATCAGTATTATGCCACAG
ACTGCTTAGATGCTTTTACATGGATCCTAAATCCGTGAAGGATTTATCACAGCATACGGTC
TTAGAAATCATTTGCACAGAAGAGTACTCAACAGGGTATACAACAAATAGCAAATAATCCA
CTTTGAAATCAAAGACAGGTTTCGCGCTTTTGTCTGGACCTCGCCTACGCAATATGGCTTCCC
TCTACGGACAGCTGGATACAACCAAGAACTCAGAGATTTCTTTACAGTCACAGACCTGAGG
ATAAGGCTGTAAAGACCAGCCGTTGGGGAAATATTTGTAGATGAGCTACACTTGGCACGCTA
CTTTTACGCGATCTCAGACATAAAGGTGCGAGGAAGGTGCAAGTGTAATCTCCATGCCACTG
TATGTGTGTATGACAACAGCAAATTGACATGCGAATGTGAGCACAACACTACAGGTCCAGAC
TGTGGGAAATGCAAGAAGAATTATCAGGGCCGACCTTGGAGTCCAGGCTCCTATCTCCCCAT
CCCCAAAGGCACTGCAAATACCTGTATCCCCAGTATTTCCAGTATTGGTACGAATGTCTGCG
ACAACGAGCTCCTGCACTGCCAGAACGGAGGGACGTGCCACAACAACGTGCGCTGCCTGTGC
CCGGCCGCATACACGGGCATCCTCTGCGAGAAGCTGCGGTGCGAGGAGGCTGGCAGCTGCGG
CTCCGACTCTGGCCAGGGCGCGCCCCCGCACGGCACCCAGCGCTGCTGCTGTGACCACGC
TGCTGGGAACCGCCAGCCCCCTGGTGTTCTAGGTGTACCTCCAGCCACACCGGACGGGCCT
GTGCCGTGGGGAAGCAGACACAACCCAAACATTTGCTACTAACATAGGAAACACACACATAC
AGACACCCCCACTCAGACAGTGTAACAACTAAGAAGGCCTAACTGAACTAAGCCATATTTAT
CACCCGTGGACAGCACATCCGAGTCAAGACTGTTAATTTCTGACTCCAGAGGAGTTGGCAGC
TGTTGATATTATCACTGCAAATCACATTGCCAGCTGCAGAGCATATTGTGGATTGGAAAGGC
TGCGACAGCCCCCAAACAGGAAAGACAAAAACAAACAAATCAACCGACCTAAAAACATTG
GCTACTCTAGCGTGCGGCCCTAGTACGACTCCGCCCAGTGTTGGACCAACCAAATAGCA
TTCTTTGCTGTGAGGTGCATTGTGGGCATAAGGAAATCTGTTACAAGCTGCCATATTGGCCT
GCTTCCGTCCCTGAATCCCTTCCAACCTGTGCTTTAGTGAACGTTGCTCTGTAACCCCTCGTT
GGTTGAAAGATTTCTTTGTCTGATGTTAGTGATGCACATGTGTAACAGCCCCCTCTAAAGC
GCAAGCCAGTCATACCCCTGTATATCTTAGCAGCACTGAGTCCAGTGCGAGCACACACCCAC
TATACAAGAGTGGCTATAGGAAAAAGAAAGTGTATCTATCCTTTTGTATTCAAATGAAGTT
ATTTTTCTTGAACTACTGTAATATGTAGATTTTTTGTATTATTGCCAATTTGTGTTACCAGA
CAATCTGTTAATGTATCTAATTGCAATCAGCAAAGACTGACATTTTATTTTGTCTCTTTTCG
TTCTGTTTTGTTTCACTGTGCAGAGATTTCTCTGTAAGGGCAACGAACGTGCTGGCATCAA
GAATATCAGTTTACATATATAACAAGTGTAAATAAGATTCCACCAAAGGACATTCTAAATGTT
TTCTTGTTGCTTTAACACTGGAAGATTTAAAGAATAAAAACTCCTGCATAAACGATTTCAGG
AATTTGTATTGCAATTTCTTAAGATGAAAGGAACAGCCACCAAGCAGTTTCACACTCACTTT
ACTGATTTCTGTGTGGACTGAGTACATTGAGCTGACGAATTTAGTTCCCAGGAAGATGGATT
GATGTTCACTAGCTTGGACAACCTTCTGCAAAATATGAGACTATTTCCACTTGGGAAAAATTA
CAACAGCAAAAAAAAAAAAAAAAAAAAAA

FIGURE 74

MYLSRSLSIHALWVTVSSVMQPYPLVWGHYDLCKTQIYTEEGKVWDYMACQPESTDMTKYLK
VKLDPPDITCGDPPETFCAMGNPYMCNNECDASTPELAHPPELMFDFEGRHPSTFWQSATWK
EYPKPLQVNITLSWSKTIELTDNIVITFESGRPDQMILEKSLDYGRTWQPYQYYATDCLDAF
HMDPKSVKDLSQHTVLEIICTEEYSTGYTTNSKIIHFEIKDRFALFAGPRLRNMASLYGQLD
TTKKLRDFFTVTDLRIRLLRPAVGEIFVDELHLARYFYAISDIKVRGRCKCNLHATVCVYDN
SKLTCECEHNTTGPDCGKCKKNYQGRPWSPGSYLPIPKGTANTCIPSISSIGTNVCDNELLH
CQNGGTCHNNVRCLCPAAYTGILCEKLRCEEAGSCGSDSGQGAPPHGTPALLLLTTLLGTAS
PLVF

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FIGURE 75

CCCACGCGTCCGGGTGACCTGGGCCGAGCCCTCCCGGTCCGGCTAAGATTGCTGAGGAGGCGG
CGGGTAGCTGGCAGGCGCCGACTTCCGAAGGCCGCGTCCGGGCGAGGTGTCCTCATGACTT
CTCTTGTGGACCATGTCGGTGATCTTTTTTGCCTGCGTGGTACGGGTAAGGGATGGACTGCC
CCTCTCAGCCTCTACTGATTTTTTACCACACCCAAGATTTTTTGGAAATGGAGGAGACGGCTCA
AGAGTTTAGCCTTGCGACTGGCCCAGTATCCAGGTGAGGTTCTGCAGAAGGTTGTGACTTT
AGTATACATTTTTCTTCTTTCGGGGACGTGGCCTGCATGGCTATCTGCTCCTGCCAGTGTCC
AGCAGCCATGGCCTTCTGCTTCCTGGAGACCCTGTGGTGGGAATTCACAGCTTCCTATGACA
CTACCTGCATTGGCCTAGCCTCCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTCAG
AAAGTGAAGTGGCATTTTAACTATGTAAGTTCCTCTCAGATGGAGTGCAGCTTGAAAAAAT
TCAGGAGGAGCTCAAGTTGCAGCCTCCAGCGGTTCTCACTCTGGAGGACACAGATGTGGCAA
ATGGGGTGATGAATGGTCACACACCGATGCACTTGGAGCCTGCTCCTAATTTCCGAATGGAA
CCAGTGACAGCCCTGGGTATCCTCTCCCTCATCTCAACATCATGTGTGCTGCCCTGAATCT
CATTCGAGGAGTTCACCTTGCAAGCATTCTTTACAGGATCCAAGGAGCTGGTTCTGCTGGT
TGGACCAAACCTCGTGAGCCAGCCACCCCTGACCCAAATGAGGAGAGCTCTGATTCTCCCAT
CCGGGAGCAGTGATGTCAAACCTTCTGCTGCTGGGGAAATCTCATCAGCAGGGAGCCTGTGGA
AAAGGGCATGTCAGTGAAATCTGGGAATGGCTGGATTCCGGAACATCTGCCCATGTGTATTG
ATGGCAGAGCTGTTGCCACACAAGCGCCTTTTATTTAGGGTAAAATTAACAAATCCATTCTAT
TCCTCTGACCCATGCTTAGTACATATGACCTTTAACCCTTACATTTATATGATTCTGGGGTT
GCTTCAGAAGTGTTATTTTCATGAATCATTCATATGATTTGATCCCCCAGGATTCTATTTTGT
TTAATGGGCTTTTCTACTAAAAGCATAAAATACTGAGGCTGATTTAGTCAGGGCAAAACCAT
TTACTTTACATATTCGTTTTCAATACTTGCTGTTTATGTTACACAAGCTTCTTACGGTTTTTC
TTGTAACAATAAATATTTTGAGTAAATAATGGGTACATTTTAACAAACTCAGTAGTACAACC
TAAACTTGTATAAAAAGTGTGTAAAAATGTATAGCCATTTATATCCTATGTATAAATTAAATG
AGGTGGCTTCAGAAATGGCAGAATAAATCTAAAGTGTTTATTAATAAAAAAAAAAAAAAAAAAA
AAAAG

FIGURE 76

MSVIFFACVVRVRDGLPLSASTDFYHTQDFLEWRRRLKSLALRLAQYPGRGSAEGCDFSIHF
SSFGDVACMAICSCQCPAAMAFCFLETLWWEFTASYDTTCIGLASRPYAFLEFDSIIQKVKW
HFNYVSSSQMECSLEKIQEELKLQPPAVLTLEDTDVANGVMNGHTPMHLEPAPNFRMEPVTA
LGILSLILNIMCAALNLIRGVHLAEHSLQDPRSWFCWLDQTS

FIGURE 77

TGCTTCCTGGAGACCCTGTGGTGGGAATTCACAGCTTCNTATGACACTACCTGCATTGGCNT
AGCCTCCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTAGAAAAGTGAAGTGGCATT
TTAACTATGTAAGTTCCTNTCAGATGGAGTGCAGCTTGAAAAAATTCAGGAGGAGCTCAAG
TTGCAGCCTCCAGCGGTTCTCANTATGGAGGACACAGATGTGGCAAATGGGGT

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FIGURE 78

CTCAGCGGCGCTTCCTCGTAGCGAGCCTAGTGCGGGTGTTTGCATTGAAACGTGAGCGCGA
CCCGACCTTTAAAGAGTGGGGAGCAAAGGGAGGACAGAGCCCTTTAAAACGAGGCGGGTGCTG
CCTGCCCCCTTTAAGGGCGGGGCGTCCGGACGACTGTATCTGAGCCCCAGACTGCCCCGAGTT
TCTGTGCGCAGGCTGCGAGGAAAGGCCCTAGGCTGGGTCTGGGTGCTTGGCGGCGGCGGCTT
CCTCCCCGCTCGTCTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTA
TGGAAGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGC
GAGTGTATTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTTCCTGAC
CCGCTTCAAGAAGCCTGCTGAGTTCACCACAGTGATGATGAAGATGCCACCGTCAACAAGA
TTGCGCTCGAGCTGTGCACCTTTACCCTGGCAATTGCCCTGGGTGCTGTCTGCTCCTGCCC
TTCTCCATCATCAGCAATGAGGTGCTGCTCTCCCTGCCTCGGAACCTACTACATCCAGTGGCT
CAACGGCTCCCTCATCCATGGCCTCTGGAACCTTGTTTTCTCTTCCCCAACCTGTCCCTCA
TCTTCTCATGCCCTTTGCATATTTCTTCACTGAGTCTGAGGGCTTTGCTGGCTCCAGAAAG
GGTGTCTGGGCCGGGTCTATGAGACAGTGGTGATGTTGATGCTCCTCACTCTGCTGGTGCT
AGGTATGGTGTGGGTGGCATCAGCCATTGTGGACAAGAACAAGGCCAACAGAGAGTCACTCT
ATGACTTTTGGGAGTACTATCTCCCCTACCTCTACTCATGCATCTCCTTCCTTGGGGTTCTG
CTGCTCCTGGTGTGTACTCCACTGGGTCTCGCCCGCATGTTCTCCGTCACTGGGAAGCTGCT
AGTCAAGCCCCGGCTGCTGGAAGACCTGGAGGAGCAGCTGTACTGCTCAGCCTTTGAGGAGG
CAGCCCTGACCCGCAGGATCTGTAATCCTACTTCTGCTGGCTGCCTTTAGACATGGAGCTG
CTACACAGACAGGTCTGGCTCTGCAGACACAGAGGGTCTGCTGGAGAAGAGGCGGAAGGC
TTCAGCCTGGCAACGGAACCTGGGCTACCCCTGGCTATGCTGTGCTTGGTGTGCTGACGG
GCCTGTCTGTGCTCATTTGTGGCCATCCACATCCTGGAGCTGCTCATCGATGAGGCTGCCATG
CCCCGAGGCATGCAGGGTACCTCCTTAGGCCAGGTCTCCTTCTCCAAGCTGGGCTCCTTTGG
TGCCGTCATTACAGTTGTACTCATCTTTTACCTAATGGTGTCTCAGTTGTGGGCTTCTATA
GCTCTCCACTCTTCCGGAGCCTGCGGCCAGATGGCACGACACTGCCATGACGCAGATAATT
GGGAACGTGTGTCTGTCTCCTGGTCCTAAGCTCAGCACTTCCTGTCTTCTCTCGAACCTGGG
GCTCACTCGCTTTGACCTGCTGGGTGACTTTGACGCTTCAACTGGCTGGGCAATTTCTACA
TTGTGTTCTCTACAACGCAGCCTTTGCAGGCCTCACCACACTCTGTCTGGTGAAGACCTTC
ACTGCAGCTGTGCGGGCAGAGCTGATCCGGGCCTTTGGGCTGGACAGACTGCCGCTGCCCGT
CTCCGGTTTCCCCCAGGCATCTAGGAAGACCCAGCACCACTGACCTCCAGCTGGGGGTGGGA
AGGAAAAAACTGGACACTGCCATCTGCTGCCTAGGCCTGGAGGGAAGCCCAAGGCTACTTGG
ACCTCAGGACCTGGAATCTGAGAGGGTGGGTGGCAGAGGGGAGCAGAGCCATCTGCACTATT
GCATAATCTGAGCCAGAGTTTGGGACCAGGACCTCCTGCTTTTCCATACTTAAGTGTGGCCT
CAGCATGGGGTAGGGCTGGGTGACTGGGTCTAGCCCCTGATCCCAAATCTGTTTACACATCA
ATCTGCCTCACTGCTGTTCTGGGCCATCCCCATAGCCATGTTTACATGATTTGATGTGCAAT
AGGGTGGGGTAGGGGCAGGGAAAGGACTGGGCCAGGGCAGGCTCGGGAGATAGATTGTCTCC
CTTGCTCTGGCCCAGCAGAGCCTAAGCACTGTGCTATCCTGGAGGGGCTTTGGACCACCTG
AAAGACCAAGGGGATAGGGAGGAGGAGGCTTCAGCCATCAGCAATAAAGTTGATCCAGGGA
AAAAAA

FIGURE 79

MEAPDYEVLSVREQLFHERIRECIISTLLFATLYILCHIFLTRFKKPAEFTTVDDDEDATVNK
IALELCTFTLAIALGAVLLLPFSIISNEVLLSLPRNYIIQWLNGSLIHGLWNLVFLFPNLSL
IFLMPFAYFFTESEGFAGSRKGVLG RVYETVVMLMLLTLLVLGMVWVASAIVDKNKANRESL
YDFWEYYPYLYSCISFLGVLLLLVCTPLGLARMFSVTGKLLVKPRLLEDLEEQLYCSAFEE
AALTRRICNPTSCWLPLDMELLHRQVLALQTQRVLLEKRRKASAWQRNLGYPLAMLCLLVLT
GLSVLIVAIHILELLIDEAAMPGRMQGTSLGQVSFSKLGSGGAVIQVVLIFYLMVSSVVGFY
SSPLFRSLRPRWHD TAMTQIIGNCVCLLVLSALPVFSRTLGLTRFDLLGDFGRFNWLGNFY
IVFLYNAAFAGLTTLCLVKTF TAAVRAELIRAFGLDRLPLPVSGFPQASRKTQHQ

FIGURE 80

GGCTGCCGAGGGAAGGCCCTTGGGTTGGTCTTGGTTGCTTGGCGGCGGCGGNTTCNTCCCC
GCTCGTCCTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTATGGAAGC
ACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGCGAGTGTA
TTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTTCCTGACCCGCTTC
AAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCG

FIGURE 81

GACCGACCTTAAAGAGTGGGAGCAAAGGGAGGACAGAGCCTTTTAAAACGAGGCGGTGGTGC
CTGCCCTTTAAGGGCGGGCGTCCGGACGACTGTATCTGAGCCCCAGACTGCCCCGAGTTTC
TGTCGCAGGCTGCGAGGAAAGGCCCTAGGCTGGGTCTGGTGCTTGCGGGCGGCGGCTTCCT
CCCCGTTGTCNTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTATGGA
AGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGCGAGT
GTATTATATCAACACTTCTGTTTGCAACACTGTACATCNTCTGCCACATCTTCCTGACCCGC
TTCAAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCGTCAACAAGATTGC
GCTCGAGCTGTGCACCTTTACCCTGGCAATTGCCCTGGGTGCTGTCCTGCTCCTGCCCTTCT
CCATCATCAGCAATGAGGTGCTGCACTCCC

FIGURE 82

GATGTGCTCCTTGGAGCTGGTGTGCAGTGTCTGACTGTAAGATCAAGTCCAAACCTGTTTT
GGAATTGAGGAACTTCTCTTTTGATCTCAGCCCTTGGTGGTCCAGGTCTTCATGCTGCTGT
GGGTGATATTACTGGTCCTGGCTCCTGTCAGTGGACAGTTTGCAAGGACACCCAGGCCCAT
ATTTTCCTCCAGCCTCCATGGACCACAGTCTTCCAAGGAGAGAGAGTGACCCTCACTTGCAA
GGGATTTTCGCTTCTACTCACCACAGAAAAACAAATGGTACCATCGGTACCTTGGGAAAGAAA
TACTAAGAGAAAACCCAGACAATATCCTTGAGGTTTCAGGAATCTGGAGAGTACAGATGCCAG
GCCAGGGCTCCCCTCTCAGTAGCCCTGTGCACTTGGATTTTTCTTCAGAGATGGGATTTCC
TCATGCTGCCCAGGCTAATGTTGAACTCCTGGGCTCAAGTGATCTGCTCACCTTAGGCCTCTC
AAAGCGCTGGGATTACAGCTTCGCTGATCCTGCAAGCTCCACTTTCTGTGTTTGAAGGAGAC
TCTGTGGTTCTGAGGTGCCGGGCAAAGGCGGAAGTAACACTGAATAATACTATTTACAAGAA
TGATAATGTCCTGGCATTCCCTTAATAAAAGAACTGACTTCCAAAAAAAAAAAAAAAAAAAAA

FIGURE 83

MLLWVILLVLAPVSGQFARTPRPIIFLQPPWTTVFQGERVTLTCKGFRFYSPQKTKWYHRYL
GKEILRETPDNILEVQESGEYRCQAQGSPLSSPVHLDFSSEMGFPHAAQANVELLGSSDLLT

FIGURE 84

CAGAAGAGGGGGCTAGCTAGCTGTCTCTGCGGACCAGGGAGACCCCCGCGCCCCCGGTGT
GAGGCGGCCTCACAGGGCCGGGTGGGCTGGCGAGCCGACGCGGCGGCGGAGGAGGCTGTGAG
GAGTGTGTGGAACAGGACCCGGGACAGAGGAACCATGGCTCCGCAGAACCTGAGCACCTTTT
GCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATAAGATCTTG
GGGGTGCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAACTAGCCCTGCA
GCTTCATCCCGACCGGAACCCTGATGATCCACAAGCCCAGGAGAAATTCCAGGATCTGGGTG
CTGCTTATGAGGTTCTGTCAGATAGTGAGAAACGGAAACAGTACGATACTTATGGTGAAGAA
GGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTTCACACTTCTTTGGGGATTT
TGTTTTTCATGTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATATTCCAAGAGGAAGTGATA
TTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAGGAAATTTTGTGGAAGTAGTT
AGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGAAGTGCAATTGTCCGCAAGAGAT
GCGGACCACCCAGCTGGGCCCTGGGCGCTTCCAAATGACCCAGGAGGTGGTCTGCGACGAAT
GCCCTAATGTCAAACCTAGTGAATGAAGAACGAACGCTGGAAGTAGAAATAGAGCCTGGGGTG
AGAGACGGCATGGAGTACCCCTTTATTGGAGAAGGTGAGCCTCACGTGGATGGGGAGCCTGG
AGATTTACGGTTCCGAATCAAAGTTGTCAAGCACCCAATATTTGAAAGGAGAGGAGATGATT
TGTACACAAATGTGACAATCTCATTAGTTGAGTCACTGGTTGGCTTTGAGATGGATATTACT
CACTTGGATGGTCACAAGGTACATATTTCCCGGGATAAGATCACCAGGCCAGGAGCGAAGCT
ATGGAAGAAAGGGGAAGGGCTCCCCAACTTTGACAACAACAATATCAAGGGCTCTTTGATAA
TCACTTTTGTATGTGGATTTTCCAAAAGAACAGTTAACAGAGGAAGCGAGAGAAGGTATCAA
CAGCTACTGAAACAAGGGTCAGTGCAGAAGGTATACAATGGACTGCAAGGATATTGAGAGTG
AATAAAATTGGACTTTGTTTAAATAAGTGAATAAGCGATATTTATTATCTGCAAGGTTTTT
TTGTGTGTGTTTTTGTTTTTATTTTCAATATGCAAGTTAGGCTTAATTTTTTTATCTAATGA
TCATCATGAAATGAATAAGAGGGCTTAAGAATTTGTCCATTTGCATTTCGAAAAGAATGACC
AGCAAAGGTTTACTAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCCTGAGT
TTCAAGAATTAAAGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGA
GTTGTTAGCAATTTTCATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTG
TTATTTT

FIGURE 85

MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRSASIKDIKKAYRKLALQLHPDRNPDDPQ
AQEKFQDLGAAYEVLSNSEKRRQYDTYGEGLKDGHQSSHGDI FSHFFGDFGFMFGGTPRQQ
DRNI PRGSDI IVDLEVTL EEVYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTTQLGPGRFQ
MTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGM EY PFIGEGEPHVDGEPGDLRFRIKVVKH
PIFERRGDDLYTNVTISLVESLVGFEMDITHLDG HKVHISRDKITRPGAKLWKKGEGLPNFD
NNNIKGSLIITFDVDFPKEQLTEEAREGIKQLLKQGSVQKVYNGLQGY

FIGURE 86

TGGGACCAGGGAACCCCGGGCCCCCGGTGGAGNGCCTAACAGGCCGGTGGNTGCGACCGAA
GCGGCGGGCGGAGGAGGTTTTGAGGATTTTTGGAACAGGACCCGGACAGAGGAACCATGGTT
CCGCAGAACNTGAGCACNTTTTGCCTGTTGNTGNTATACTTCATCGGGGCGGTGATTGCCGG
ACGAGATTTNTATAAGATTTTGGGGTGCCCTNGAAGTGCCTTNTATAAAGGATATTAAAAAGG
CCTATAGGAACTAGCCCTGCAGNTTATCCCGACCGGAACCCTGATGATCCACAAGCCCAG
GAGAAATTCCAGGATTTGGGTGCTGCTTATGAGGTTNTGTCAGATAGTGAGAAACGGAAACA
GTACGATAATTATGGTGAAGAAGGATTAAAAGATGGTNATCAGAGCTCCCATGGAGACATTT
TTTCACACTTNTTTGGGGATTTTGGTTTCATGTTTGGAGGAACCCCTNGTCAGCAAGACAGA
AATATTCCAAGAG

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FIGURE 87

GGCACGAGGCGGCGGGGAGTCGCGGGATGCGCCCGGAGCCACAGCCTGAGGCCCTCAGGT
CTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTTGCCACTTCCA
GCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAAGCATGG
AGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGTTTGCAGCC
TTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGGCCGCGAGACCTGCTGCAGCGCTATGATTTC
TAAGCCCATTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCTCTGAGTTAGAAC
TGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGAATGAAGACTGGATC
GAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGATTTGTCACACTCTGAC
AGAGAAGCTTGTTGCCATGACAATGGGCTCTGGGGCCAAGATGAAGACTTCAGCCAGTGTCA
GCGACATCATTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGGATGATGTTGTGAAGTCGATG
TACCCTCCGTTGGACCCCAAACCTCTGGACGCACGGACGACTGCCCTGCTCCTGTCTGTCAG
TCACCTGGTGCTGGTGACAAGGAATGCCTGCCATCTGACGGGAGGCCTGGACTGGATTGACC
AGTCTCTGTGCGCTGCTGAGGAGCATTTGGAAGTCCTTCGAGAAGCAGCCCTAGCTTCTGAG
CCAGATAAAGGCCCTCCCAGGCCCTGAAGGCTTCTGCAGGAGCAGTCTGCAATTTAGTGCCT
ACAGGCCAGCAGCTAGCCATGAAGGCCCTGCCGCCATCCCTGGATGGCTCAGCTTAGCCTT
CTACTTTTTCCTATAGAGTTAGTTGTTCTCCACGGCTGGAGAGTTCAGCTGTGTGTGCATAG
TAAAGCAGGAGATCCCCGTCAGTTTATGCCTCTTTTGCAGTTGCAAACGTGGCTGGTGAGT
GGCAGTCTAATACTACAGTTAGGGGAGATGCCATTCACCTCTCTGCAAGAGGAGTATTGAAAA
CTGGTGGACTGTGAGCTTTATTTAGCTCACCTAGTGTTTTCAAGAAAATTGAGCCACCGTCT
AAGAAATCAAGAGGTTTACATTAAATTAGAATTTCTGGCCTCTCTCGATCGGTGAGAATG
TGTGGCAATTCTGATCTGCATTTTCAGAAGAGGACAATCAATTGAAACTAAGTAGGGGTTTC
TTCTTTTGGCAAGACTTGTAATCTCTCACCTGGCCTGTTTCATTTATTTGTATTATCTGCCT
GGTCCCTGAGGCGTCTGGGTCTCTCCTCTCCCTTGACAGGTTTGGGTTTGAAGCTGAGGAACT
ACAAAGTTGATGATTTCTTTTTTATCTTTATGCCTGCAATTTTACCTAGCTACCACTAGGTG
GATAGTAAATTTATACTTATGTTTCCCTCAAAAAAAAAAAAAA

FIGURE 88

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPSSEL
ELDDVVITNPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMKTSAS
VSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLSVSHLVLVTRNACHLTGGLDWI
DQSLSAEEHLEVLREAALASEPDKGLPGPEGFLQEQAISAI

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FIGURE 89

GCTTCATTTCTCCCGACTCAGCTTCCCACCCTGGGCTTCCGAGGTGCTTTCGCCGCTGTCC
CCACCACTGCAGCCATGATCTCCTTAACGGACACGCAGAAAATTGGAATGGGATTAACAGGA
TTTGGAGTGTTTTCTGTTCTTTGGAATGATTCTCTTTTTTGACAAAGCACTACTGGCTAT
TGGAAATGTTTTATTTGTAGCCGGCTTGGCTTTTGTAATTGGTTTAGAAAGAACATTCAGAT
TCTTCTTCCAAAAACATAAAATGAAAGCTACAGGTTTTTTTTCTGGGTGGTGTATTTGTAGTC
CTTATTGGTTGGCCTTTGATAGGCATGATCTTCGAAATTTATGGATTTTTCTCTTGTTTCAG
GGGCTTCTTCTGTGTCGTTGTTGGCTTTATTAGAAGAGTGCCAGTCCTTGGATCCCTCCTAAAT
TTACCTGGAATTAGATCATTTGTAGATAAAGTTGGAGAAAGCAACAATATGGTATTAACAACA
AGTGAATTTGAAGACTCATTTAAAATATTGTGTTATTTATAAAGTCATTTGAAGAATATTCA
GCACAAAATTAAATTACATGAAATAGCTTGTAATGTTCTTTACAGGAGTTTAAACGTATAG
CCTACAAAGTACCAGCAGCAAATTAGCAAAGAAGCAGTGAAAACAGGCTTCTACTCAAGTGA
ACTAAGAAGAAGTCAGCAAGCAAAGTGAAGAGAGGTGAAATCCATGTTAATGATGCTTAAGAA
ACTCTTGAAGGCTATTTGTGTTGTTTTCCACAATGTGCGAAACTCAGCCATCCTTAGAGAA
CTGTGGTGCCCTGTTTCTTTCTTTTTATTTTGAAGGCTCAGGAGCATCCATAGGCATTTGCT
TTTTAGAAGTGTCCTGCAATGGCAAAAATATTTCCAGTTGCACTGTATCTCTGGAAGTGA
TGCATGAATTCGATTGGATTGTGTCATTTTAAAGTATTAAAACCAAGGAAACCCCAATTTTG
ATGTATGGATTACTTTTTTTTTGNGCNCAGGGCC

FIGURE 90

MISLTDQTQKIGMGLTGFGVFFLFFGMILFFDKALLAIGNVLFVAGLAFVIGLERTFRFFFQK
HKMKATGFFLGGVFVVLIGWPLIGMIFEIYGFFLLFRGFFPVVVGFIIRVPVLGSLNLPGI
RSFVDKVGESNNMV

Important features:**Transmembrane domains:**

amino acids 12-30 (typeII), 33-52, 69-89 and 93-109

N-myristoylation sites.

amino acids 11-16, 51-56 and 116-121

Aminoacyl-transfer RNA synthetases class-II protein.

amino acids 49-59

FIGURE 91

GAAGACGTGGCGGCTCTCGCCTGGGCTGTTTCCCGGCTTCATTTCTCCCGACTCAGCTTCCC
ACCNTGGGCTTTCCGAGGTGCTTTCGCCGCTGTCCCCACCACTGCAGCCATGATCTCCTTAA
CGGACACGCAGAAAATTGGAATGGGATTAACCGGATTTGGAGTGTTTTTCCTGTTCTTTGGA
ATGATTCTCTTTTTTGACAAAGCACTACTGGCTATTGGAAATGTTTTATTTGTAGCCGGCTT
GGCTTTTGTAATTGGTTTAGAAAGAACATTCAGATTCTTCTTCCAAAAACATAAAATGAAAG
CTACAGGTTTTTTTCTGGGTGGTGTATTTGTAGTCCTTATTGGTTGGCCTTTGATAGGCATG
ATCTTCGAAATTTATGGATTTTTTCTCTTGTTT

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FIGURE 92

GGCACGAGGCTGAACCCAGCCGGCTCCATCTCAGCTTCTGGTTTCTAAGTCCATGTGCCAAA
GGCTGCCAGGAAGGAGACGCCTTCCTGAGTCCTGGATCTTCTTCTTCTGGAATCTTTGA
CTGTGGGTAGTTATTTATTTCTGAATAAGAGCGTCCACGCATCATGGACCTCGCGGGACTGC
TGAAGTCTCAGTTCCTGTGCCACCTGGTCTTCTGCTACGTCTTTATTGCCTCAGGGCTAATC
ATCAACACCATTTCAGCTCTTCACTCTCCTCCTCTGGCCCATTAACAAGCAGCTCTTCCGGAA
GATCAACTGCAGACTGTCCTATTGCATCTCAAGCCAGCTGGTGATGCTGCTGGAGTGGTGGT
CGGGCACGGAATGCACCATCTTCACGGACCCGCGCGCCTACCTCAAGTATGGGAAGGAAAAT
GCCATCGTGGTTCTCAACCACAAGTTTGAAATTGACTTTCTGTGTGGCTGGAGCCTGTCCGA
ACGCTTTGGGCTGTTAGGGGGCTCCAAGGTCTTGCCAAGAAAGAGCTGGCCTATGTCCCAA
TTATCGGCTGGATGTGGTACTTCACCGAGATGGTCTTCTGTTTCGCGCAAGTGGGAGCAGGAT
CGCAAGACGGTTGCCACCAGTTTGACGACCTCCGGGACTACCCCGAGAAGTATTTTTTCTCT
GATTCACTGTGAGGGCACACGGTTCACGGAGAAGAAGCATGAGATCAGCATGCAGGTGGCCC
GGGCCAAGGGGCTGCCTCGCCTCAAGCATCACCTGTTGCCACGAACCAAGGGCTTCGCCATC
ACCGTGAGGAGCTTGAGAAATGTAGTTTCAGCTGTATATGACTGTACACTCAATTTTCAAGAA
TAATGAAAATCCAACACTGCTGGGAGTCCTAAACGGAAAGAAATACCATGCAGATTTGTATG
TTAGGAGGATCCCCTGGAAGACATCCCTGAAGACGATGACGAGTGCTCGGCCTGGCTGCAC
AAGCTCTACCAGGAGAAGGATGCCTTTTACGAGGAGTACTACAGGACGGGCACCTTCCCAGA
GACGCCCATGGTGCCCCCCCCGGCGGCCCTGGACCCTCGTGAAGTGGCTGTTTTGGGCCTCGC
TGGTGCTCTACCCTTTCTTCCAGTTCTCTGGTCAGCATGATCAGGAGCGGGTCTTCCCTGACG
CTGGCCAGCTTCATCCTCGTCTTCTTTGTGGCCTCCGTGGGAGTTCGATGGATGATTGGTGT
GACGGAAATTGACAAGGGCTCTGCCTACGGCAACTCTGACAGCAAGCAGAACTGAATGACT
GACTCAGGGAGGTGTCACCATCCGAAGGGAACCTTGGGGAAGTGGTGGCCTCTGCATATCCT
CCTTAGTGGGACACGGTGACAAAGGCTGGGTGAGCCCCGCTGGGCACGGCGGAAGTCACGA
CCTCTCCAGCCAGGGAGTCTGGTCTCAAGGCCGATGGGGAGGAAGATGTTTTGTAATCTTT
TTTTCCCCATGTGCTTTAGTGGGCTTTGGTTTTCTTTTTGTGCGAGTGTGTGTGAGAATGGC
TGTGTGGTGAGTGTGAAGTTTGTCTGTGATCATAGAAAGGGTATTTTAGGCTGCAGGGGAG
GGCAGGGCTGGGGACCGAAGGGGACAAGTTCCCTTTTCATCCTTTGGTGCTGAGTTTTCTGT
AACCCTTGGTTGCCAGAGATAAAGTGAAAAGTGCTTTAGGTGAGATGACTAAATTATGCCTC
CAAGAAAAAAAAAATTAAAGTGCTTTTCTGGGTCAAAAAAAAAA

FIGURE 93

MDLAGLLKSQFLCHLVFCYVFIA SGLIINTIQFLTLLLPINKQLFRKINCRLSYCISSQLV
MLLEWWSGTECTIFTDPRAYLKYGKENAIVVLNHKFEIDFLCGWSLSERFGLLGGSKVLAKK
ELAYVPIIGWMWYFTEMVFC SRKWEQDRKTVATSLQH LRDYPEKYFFLIHCEGTRFTEKKHE
ISMQVARAKGLPRLKHLLPRTKGFAITVRSLRNVVSAVYDCTLNFRNNENPTLLGVLNGKK
YHADLYVRRIPLEDIPEDDDDECSAWLHKLYQEKDAFQEEYYRTGTFFETPMVPPRRPWTLVN
WLFWASLVLYPFFQFLVSMIRSGSSLTLASFILVFFVASVGVRWMIGVTEIDKGSAYGNSDS
KQKLND

FIGURE 94

CTGAGGCGGCGGTAGCATGAGGGGGAGAGTACGTCGGCGGTGCTCTCGGGCTTTGTGCTCG
GCGCACTCGCTTTCCAGCACCTCAACACGGAAGGTTTCTTCTTGGGGAA
GTAAAAGGTGAAGCCAAGAACAGCATTACTGATTCCCAAATGGATGATGTTGAAGTTGTTTA
TACAATTGACATTCAGAAATATATTCCATGCTATCAGCTTTTGTAGCTTTTATAATTCTTCAG
GCGAAGTAAATGAGCAAGCACTGAAGAAAATATTATCAAATGTCAAAAAGAATGTGGTAGGT
TGGTACAAATTCGGTCGTCATTGAGATCAGATCATGACGTTTAGAGAGAGGCTGCTTCACAA
AACTTGCAGGAGCATTTTTCAAACCAAGACCTGTTTTTCTGCTATTAACACCAAGTATAA
TAACAGAAAGCTGCTCTACTCATCGACTGGAACATTCTTATATAAACCTCAAAAAGGACTT
TTTCACAGGGTACCTTTAGTGGTTGCCAATCTGGGCATGTCTGAACAACTGGGTTATAAAAC
TGTATCAGGTTCTGTATGTCCACTGGTTTTAGCCGAGCAGTACAAACACACAGCTCTAAAT
TTTTTGAAGAAGATGGATCCTTAAAGGAGGTACATAAGATAAATGAAATGTATGCTTCATTA
CAAGAGGAATTAAAGAGTATATGCAAAAAAGTGGAAGACAGTGAACAAGCAGTAGATAAACT
AGTAAAGGATGTAAACAGATTAAAACGAGAAATTGAGAAAAGGAGAGGAGCACAGATTCAGG
CAGCAAGAGAGAAGAACATCCAAAAGACCCTCAGGAGAACATTTTTCTTTGTCAGGCATTA
CGGACCTTTTTTCCAAATCTGAATTTCTTCATTCATGTGTTATGTCTTTAAAAAATAGACA
TGTTTTCTAAAAGTAGCTGTAACTACAACCACCATCTCGATGTAGTAGACAATCTGACCTTAA
TGGTAGAACACACTGACATTCCTGAAGCTAGTCCAGCTAGTACACCACAAATCATTAAAGCAT
AAAGCCTTAGACTTAGATGACAGATGGCAATTCAAGAGATCTCGGTTGTTAGATACACAAGA
CAAACGATCTAAAGCAAATACTGGTAGTAGTAACCAAGATAAAGCATCCAAAATGAGCAGCC
CAGAAACAGATGAAGAAATTGAAAAGATGAAGGGTTTTGGTGAATATTCACGGTCTCCTACA
TTTTTGAATCCTTTTAACTTACAAGGAGATTTTTTTATTTGGCTGATGGGTAAAGCCAAACAT
TTCTATTGTTTTTACTATGTTGAGCTACTTGACAGTAAGTTCATTTGTTTTTACTATGTTTAC
CTGTTTGCAGTAATACACAGATAACTCTTAGTGCAATTTACTTCACAAAGTACTTTTTCAAAC
ATCAGATGCTTTTATTTCCAAACCTTTTTTTTACCTTTCACCTAAGTTGTTGAGGGGAAGGCT
TACACAGACACATTCTTTAGAATTGGAAAAGTGAGACCAGGCACAGTGGCTCACACCTGTAA
TCCCAGCACTTAGGGAAGACAAGTCAGGAGGATTGATTGAAGCTAGGAGTTAGAGACCAGCC
TGGGCAACGTATTGAGACCATGTCTATTAAAAAATAAAATGGAAAAGCAAGAATAGCCTTAT
TTTCAAAATATGGAAAGAAATTTATATGAAAATTTATCTGAGTCATTAAATTTCTCCTTAAG
TGATACTTTTTTAGAAGTACATTATGGCTAGAGTTGCCAGATAAAATGCTGGATATCATGCA
ATAAATTTGCAAAACATCATCTAAATTTAAAAAAAAAAAAAAAAAAAAA

FIGURE 95

MEGESTSAVLSGFVLGALAFQHLNTSDTEGFLGGEVKGEAKNSITDSQMDDVEVVYTIDIQ
KYIPCYQLFSFYNSSGEVNEQALKKILSNVKKNVVGWYKFRRHSDQIMTFRERLLHKNLQEH
FSNQDLVFLLLTPSIITESCSTHRLEHSLYKPQKGLFHRVPLVVANLGMSEQLGYKTVSGSC
MSTGFSRAVQTHSSKFFEEEDGSLKEVHKINEMYASLQEELKSICKKVEDSEQAVDKLVKDVN
RLKREIEKRRGAQIQAAREKNIQKDPQENIFLCQALRTFFPNSEFLHSCVMSLKNRHVSKSS
CNYNHHLDVVDNLTLMVEHTDIPEASPASTPQIIKHKALDLDLDRWQFKRSRLDLDQDKRSKA
NTGSSNQDKASKMSSPETDEEIEKMKGFGEYSRSPTF

FIGURE 96

GGCACAGCCGCGCGGCGGAGGGCAGAGTCAGCCGAGCCGAGTCCAGCCGGACGAGCGGACCA
GCGCAGGGCAGCCCAAGCAGCGCGCAGCGAACGCCCGCCGCCACACCCTCTGCGGTCC
CCGCGGCGCCTGCCACCCTTCCCTCCTTCCCCGCGTCCCCGCGCTCGCCGGCCAGTCAGCTTG
CCGGGTTCGCTGCCCCGCGAAACCCCGAGGTCACCAGCCCGCGCCTCTGCTTCCCTGGGCGG
CGCGCCGCTCCACGCCCTCCTTCTCCCTGGCCCCGGCGCCTGGCACCAGGGGACCGTTGCCT
GACGCGAGGCCCAGCTCTACTTTTCGCCCCGCGTCTCCTCCGCTGCTCGCCTCTTCCACCA
ACTCCAACCTCCTTCTCCCTCCAGCTCCACTCGCTAGTCCCCGACTCCGCCAGCCCTCGGCCC
GCTGCCGTAGCGCCGCTTCCCGTCCGGTCCCAAAGGTGGGAACGCGTCCGCCCGGCCCCGCA
CCATGGCAGCGTTTCGGCTTGCCCGCGCTTCTCTGCACCCTGGCAGTGCTCAGCGCCGCGCTG
CTGGCTGCCGAGCTCAAGTCGAAAAGTTGCTCGGAAGTGCGACGTCTTTACGTGTCCAAAGG
CTTCAACAAGAACGATGCCCCCTCCACGAGATCAACGGTGATCATTTGAAGATCTGTCCCC
AGGGTTCTACCTGCTGCTCTCAAGAGATGGAGGAGAAGTACAGCCTGCAAAGTAAAGATGAT
TTCAAAGGTGTGGTCAGCGAACAGTGCAATCATTTGCAAGCTGTCTTTGCTTCACGTTACAA
GAAGTTTGATGAATTCTTCAAAGAACTACTTGAAAATGCAGAGAAATCCCTGAATGATATGT
TTGTGAAGACATATGGCCATTTATACATGAAAATTCTGAGCTATTTAAAGATCTCTTCGTA
GAGTTGAAACGTTACTACGTGGTGGGAAATGTGAACCTGGAAGAAATGCTAAATGACTTCTG
GGCTCGCCTCCTGGAGCGGATGTTCCGCTGGTGAACCTCCAGTACCACTTTACAGATGAGT
ATCTGGAATGTGTGAGCAAGTATACGGAGCAGCTGAAGCCCTTCGGAGATGTCCCTCGCAA
TTGAAGCTCCAGGTTACTCGTGCTTTTGTAGCAGCCCGTACTTTCGCTCAAGGCTTAGCGGT
TGCGGGAGATGTGCTGAGCAAGGTCTCCGTGGTAAACCCACAGCCAGTGTAACCATGCCC
TGTTGAAGATGATCTACTGCTCCCACTGCCGGGGTCTCGTGACTGTGAAGCCATGTTACAAC
TACTGCTCAAACATCATGAGAGGCTGTTTGGCCAACCAAGGGGATCTCGATTTTGAATGGAA
CAATTTTCATAGATGCTATGCTGATGGTGGCAGAGAGGCTAGAGGGTCCTTTCAACATTGAAT
CGGTCATGGATCCCATCGATGTGAAGATTTCTGATGCTATTATGAACATGCAGGATAATAGT
GTTCAAGTGTCTCAGAAGGTTTTCCAGGGATGTGGACCCCCCAAGCCCTCCAGCTGGACG
AATTTCTCGTTCCATCTCTGAAAGTGCCTTCAGTGCTCGCTTCAGACCACATCACCCCGAGG
AACGCCCAACCAAGCAGCTGGCACTAGTTTGGACCGACTGGTTACTGATGTCAAGGAGAAA
CTGAAACAGGCCAAGAAATTCTGGTCCTCCCTTCCGAGCAACGTTTGAACGATGAGAGGAT
GGCTGCAGGAAACGGCAATGAGGATGACTGTTGGAATGGGAAAGGCAAAGCAGGTACCTGT
TTGCAGTGACAGGAAATGGATTAGCCAACCAGGGCAACAACCCAGAGGTCCAGGTTGACACC
AGCAAACAGACATACTGATCCTTCGTCAAATCATGGCTCTTCGAGTGATGACCAGCAAGAT
GAAGAATGCATACAATGGGAACGACGTGGACTTCTTTGATATCAGTGATGAAAGTAGTGGAG
AAGGAAGTGGAAAGTGGCTGTGAGTATCAGCAGTGCCCTTCAGAGTTTGACTACAATGCCACT
GACCATGCTGGGAAGAGTGCCAATGAGAAAGCCGACAGTGCTGGTGTCCGTCTGGGGCACA
GGCCTACCTCCTCACTGTCTTCTGCATCTTGTTCTGGTTATGCAGAGAGAGTGGAGATAAT
TCTCAAACCTCTGAGAAAAAGTGTTTCATCAAAAAGTTAAAGGCACCAGTTATCACTTTTCTA
CCATCCTAGTGACTTTTGCTTTTTTAAATGAATGGACAACAATGTACAGTTTTTACTATGTGGC
CACTGGTTTAAAGAAGTGCTGACTTTGTCTTCTCATTTCAGTTTTTGGGAGGAAAAGGGACTGTG
CATTGAGTTGGTTCTGCTCCCCCAAACCATGTTAAACGTGGCTAACAGTGATAGGTACAGAA
CTATAGTTAGTTGTGCATTTGTGATTTTATCACTCTATTATTGTTTGTATGTTTTTTCTC
ATTTTCGTTTGTGGGTTTTTTTTTCCAACGTGTGATCTCGCCTTGTTTCTTACAAGCAAACAG
GGTCCCTTCTTGGCACGTAAACATGTACGTATTTCTGAAATATTAAATAGCTGTACAGAAGCA
GGTTTTATTTATCATGTTATCTTATTAAAGAAAAGCCCAAAAAGC

FIGURE 97

MARFGLPALLCTLAVLSAALLAAELKSKSCSEVRRRLYVSKGFNKNDAPLHEINGDHLKICPQ
GSTCCSQEMEEKYSLQSKDDFKSVVSEQCNHLQAVFASRYKKFDEFFKELLENAAEKSLNDMF
VKTYGHLVMQNSSELFVDLVELKRYVVGNNLEEMLNDFWARLLERMFRVNSQYHFTDEY
LECVSKYTEQLKPFQDVPRKLKLQVTRAFVAARTFAQGLAVAGDVVSKVSVVNPTAQCTHAL
LKMIYCSHCRGLVTVKPCYNYCSNIMRGCLANQGDLDFEWNNFIDAMLMVAERLEGPFNIES
VMDPIDVKISDAIMNMQDNSVQVSQKVFQGCQPPKPLPAGRISRSISESAFSARFRPHHPEE
RPTTAAGTSLDRLVTDVKEKLKQAKKFWSSLPSNVCNDERMAAGNGNEDDCWNGKKGKSRYL
AVTGNGLANQGNNPEVQVDTSKPDILILRQIMALRVMTSKMKNAYNNGNDVDFFDISDESSGE
GSGSGCEYQQCPSEFDYNATDHAGKSANEKADSAGVRPGAQAYLLTVFCILFLVMQREWR

FIGURE 98

CTCGCCCTCAAATGGGAACGCTGGCCTGGGACTAAAGCATAGACCACCAGGCTGAGTATCCT
GACCTGAGTCATCCCCAGGGATCAGGAGCCTCCAGCAGGGAACCTTCCATTATATTCTTCAA
GCAACTTACAGCTGCACCGACAGTTGCGATGAAAGTTCTAATCTCTTCCCTCCTCCTGTTGC
TGCCACTAATGCTGATGTCCATGGTCTCTAGCAGCCTGAATCCAGGGGTCGCCAGAGGCCAC
AGGGACCGAGGCCAGGCTTCTAGGAGATGGCTCCAGGAAGGCGGCCAAGAATGTGAGTGCAA
AGATTGGTTCCTGAGAGCCCCGAGAAGAAAATTCATGACAGTGTCTGGGCTGCCAAAGAAGC
AGTGCCCCTGTGATCATTTCAAGGGCAATGTGAAGAAAACAAGACACCAAAGGCACCACAGA
AAGCCAAACAAGCATTCCAGAGCCTGCCAGCAATTTCTCAAACAATGTCAGCTAAGAAGCTT
TGCTCTGCCTTTGTAGGAGCTCTGAGCGCCCACTCTTCCAATTAAACATTCTCAGCCAAGAA
GACAGTGAGCACACCTACCAGACACTCTTCTTCTCCACCTCACTCTCCCACTGTACCCACC
CCTAAATCATTCCAGTGCTCTCAAAAAGCATGTTTTTCAAGATCATTTTGTTTGTTGCTCTC
TCTAGTGTCTTCTTCTCTCGTCAGTCTTAGCCTGTGCCCTCCCCTTACCCAGGCTTAGGCTT
AATTACCTGAAAGATTCCAGGAACTGTAGCTTCCTAGCTAGTGTCATTTAACCTTAAATGC
AATCAGGAAAGTAGCAAACAGAAGTCAATAAATATTTTTAAATGTCAAAAAAAAAAAAAAAAAA

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FIGURE 99

MKVLISSLLLLLPLMLMSMVSSSLNPGVARGHRDRGQASRRWLQEGGQECECKDWFLRAPRR
KFMTVSGLPKKQPCDHFKGNVKKTRHQRHHRKPNKHSRACQQLKQCQLRSFALPL

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FIGURE 100

AATGGCTGTCTTAGTACTTCGCCTGACAGTTGTCCTGGGACTGCTTGTCTTATTCCTGACCT
GCTATGCAGACGACAAACCAGACAAGCCAGACGACAAGCCAGACGACTCGGGCAAAGACCCA
AAGCCAGACTTCCCCAAATTCCTAAGCCTCCTGGGCACAGAGATCATTGAGAATGCAGTCGA
GTTTCATCCTCCGCTCCATGTCCAGGAGCACAGGATTTATGGAATTTGATGATAATGAAGGAA
AACATTTCATCAAAGTGACATCCTCAGGACACACCCATGTGGCTCCTGGACAATCCAAGAGCA
GCCAAATCCTGCTTTTCCAGTTTGGCTCCACAAGTCCTCCAGGACAGAGCCCTCAAAGCAAC
TCCCAACGAGTTCTCAGGATTCAGGCTCTGGCTTCAACCAAACAGAACTCATTTTGAACACC
CTGACTGCATTTTTGCTTTTAGAAAGTTAGAATAAATATGGCGCTTTGGGATCACATAGTTG
ATGGAGAGGAAA

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FIGURE 101

MAVLVLRLTVVLGLLVFLTCYADDKPKDPDDKPDGKDPKPDFPKFLSLLGTEIIENAVE
FILRSMRSTGFMEFDDNEGKHSSK

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FIGURE 102

GGACGCCAGCGCCTGCAGAGGCTGAGCAGGGAAAAAGCCAGTGCCCCAGCGGAAGCACAGCT
CAGAGCTGGTCTGCCATGGACATCCTGGTCCCCTCCTGCAGCTGCTGGTGCTGCTTCTTAC
CCTGCCCCCTGCACCTCATGGCTCTGCTGGGCTGCTGGCAGCCCCCTGTGCAAAAGCTACTTCC
CCTACCTGATGGCCGTGCTGACTCCCAAGAGCAACCGCAAGATGGAGAGCAAGAAACGGGAG
CTCTTCAGCCAGATAAAGGGGCTTACAGGAGCCTCCGGGAAAGTGGCCCTACTGGAGCTGGG
CTGCGGAACCGGAGCCAACTTTAGTTCTACCCACCGGGCTGCAGGGTCACCTGCCTAGACC
CAAATCCCCACTTTGAGAAGTTCTTGACAAAGAGCATGGCTGAGAACAGGCACCTCCAATAT
GAGCGGTTTGTGGTGGCTCCTGGAGAGGACATGAGACAGCTGGCTGATGGCTCCATGGATGT
GGTGGTCTGCACTCTGGTGCTGTGCTCTGTGCAGAGCCCAAGGAAGGTCCTGCAGGAGGTCC
GGAGAGTACTGAGACCGGGAGGTGTGCTCTTTTTCTGGGAGCATGTGGCAGAACCATATGGA
AGCTGGGCCTTCATGTGGCAGCAAGTTTTCTGAGCCCACCTGGAAACACATTGGGGATGGCTG
CTGCCTCACCAGAGAGACCTGGAAGGATCTTGAGAACGCCCAGTTCTCCGAAATCCAAATGG
AACGACAGCCCCCTCCCTTGAAGTGGCTACCTGTTGGGCCCCACATCATGGGAAAGGCTGTC
AAACAATCTTTCCCAAGCTCCAAGGCACTCATTTGCTCCTTCCCCAGCCTCCAATTAGAACA
AGCCACCCACCAGCCTATCTATCTTCCACTGAGAGGGACCTTAGCAGAATGAGAGAAGACATT
CATGTACCACCTACTAGTCCCTCTCTCCCCAACCTCTGCCAGGGCAATCTCTAACTTCAATC
CCGCCTTCGACAGTGAAAAAGCTCTACTTCTACGCTGACCCAGGGAGGAAACACTAGGACCC
TGTTGTATCCTCAACTGCAAGTTTCTGGACTAGTCTCCCAACGTTTGCCTCCCAATGTTGTC
CCTTTCCTTCGTTCCCATGGTAAAGCTCCTCTCGCTTTCCTCCTGAGGCTACACCCATGCGT
CTCTAGGAACTGGTCACAAAAGTCATGGTGCCTGCATCCCTGCCAAGCCCCCTGACCCTCT
CTCCCCACTACCACCTTCTTCTGAGCTGGGGGCACCAGGGAGAATCAGAGATGCTGGGGAT
GCCAGAGCAAGACTCAAAGAGGCAGAGGTTTTGTTCTCAAATATTTTTTAATAAATAGACGA
AACCACG

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FIGURE 103

MDILVPLLQLLVLLLTLPPLHLMALLGCWQPLCKSYFPYLMAVLTPKSNRKMESKKRELFSQL
KGLTGASGKVALLELGCGTGANFQFYPPGCRVTCLDPNPHFEKFLTKSMAENRHLQYERFVV
APGEDMRQLADGSMDVVVCTLVLCVQSPRKVLQEVRRVLRPGGVLFWEHVAEPYGSWAFM
WQQVFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKWLPVGPHIMGKAVKQSFP
SSKALICSFPSLQLEQATHQPIYLPLRGT

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FIGURE 104

GTGGGATTTATTTGAGTGCAAGATCGTTTTCTCAGTGGTGGTGGAAAGTTGCCTCATCGCAGG
CAGATGTTGGGGCTTTGTCCGAACAGCTCCCCCTCTGCCAGCTTCTGTAGATAAGGGTTAAAA
ACTAATATTTATATGACAGAAGAAAAAGATGTCATTCCGTAAAGTAAACATCATCATCTTGG
TCCTGGCTGTTGCTCTCTTCTTACTGGTTTTGCACCATAACTTCCTCAGCTTGAGCAGTTTG
TTAAGGAATGAGGTTACAGATTGAGGAATTGTAGGGCCTCAACCTATAGACTTTGTCCCAA
TGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCCGTGTGGTCATCGCTGCATCTG
AAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTGAGCACAACACTCGCTCCAAT
GTGATTTTCTACATTGTTACTCTCAACAATACAGCAGACCATCTCCGGTCTGGCTCAACAG
TGATTCCCTGAAAAGCATCAGATACAAAATTGTCAATTTTGACCCTAAACTTTTGGAAGGAA
AAGTAAAGGAGGATCCTGACCAGGGGGAATCCATGAAACCTTTAACCTTTGCAAGGTTCTAC
TTGCCAATTCTGGTTCCTCAGCGCAAAGAAGGCCATATACATGGATGATGATGTAATTGTGCA
AGGTGATATTCTTGCCCTTTACAATACAGCACTGAAGCCAGGACATGCAGCTGCATTTTTCAG
AAGATTGTGATTGAGCCTCTACTAAAGTTGTGATCCGTGGAGCAGGAAACCAGTACAATTAC
ATTGGCTATCTTGACTATAAAAAGGAAAGAATTTCGTAAGCTTTCCATGAAAGCCAGCACTTG
CTCATTTAATCCTGGAGTTTTTGTGCAACCTGACGGAATGGAAACGACAGAATATAACTA
ACCAACTGGAAAAATGGATGAAACTCAATGTAGAAGAGGGACTGTATAGCAGAACCCTGGCT
GGTAGCATCACAACACCTCCTCTGCTTATCGTATTTTATCAACAGCACTCTACCATCGATCC
TATGTGGAATGTCCGCCACCTTGGTTCCAGTGCTGGAAAACGATATTCACCTCAGTTTGTA
AGGCTGCCAAGTTACTCCATTGGAATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATAT
ACTGATGTTTGGGAAAAATGGTATATTCCAGACCCAACAGGCAAATTCAACCTAATCCGAAG
ATATACCGAGATCTCAAACATAAAGTGAAACAGAATTTGAACTGTAAGCAAGCATTCTCAG
GAAGTCCTGGAAGATAGCATGCATGGGAAGTAACAGTTGCTAGGCTTCAATGCCTATCGGTA
GCAAGCCATGGAAAAAGATGTGTCAGCTAGGTAAAGATGACAACTGCCCTGTCTGGCAGTC
AGCTTCCCAGACAGACTATAGACTATAAATATGTCTCCATCTGCCTTACCAAGTGTTTTCTT
ACTACAATGCTGAATGACTGGAAAGAAGAAGTATGAGCTAGTTGAGCTAGCTGGTACAGA
TAATTCAAACTGCTGTTGGTTTTAATTTTGTAACCTGTGGCCTGATCTGTAAATAAACTT
ACATTTTTC

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FIGURE 105

MSFRKVNIIILVLAVALFLLVLHHNFLSLSSLLRNEVTDSGIVGPQPIDFVPNALRHAVDGR
QEEIPVVIAASEDRLGGAIAAINSIOHNTRSNVIFYIVTLNNTADHLRSWLNSDSLKSIRYK
IVNFDPKLLEGKVKEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIVQGDILALYNT
ALKPGHAAAFSEDCDSASTKVVIRGAGNQYNYIGYLDYKKERIRKLSMKASTCSFNPGVFVA
NLTEWKRQONITNQLEKWMKLNVEEGLYSRTLGSITTPPLLIVFYQQHSTIDPMWNVRHLGS
SAGKRYSPQFVKAALLHWNGHLKPWGRTASYTDVWEKWYIPDPTGKFNLIRRYTEISNIK

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FIGURE 106

TGGTTTTTGCCCCATAAATTCCTCAGCTTGAGCAGTTTGTTAAGGAATGAGGTTACAGATT
CAGGAATTNTAGGNCCTCAACCTNTAGANTTTGTCCCAAATGTTCTCCGACATGCAGTAGAT
GGGAGACAAGAGGAGATTCTGTGGTCATCGCTGCATNTGAAGACAGGCTTGGGGGGGCCAT
TGCAGCTATAAACAGCATTCAGCACAACTCGNTCCAATGTGATTTTCTACATTGTTACTC
TCAACAATACAGCAGACCATNTCCGGTCCTGGNTCAACAGTGATTCCCTGAAAAGCATCAGA
TACAAAATTGTCAATTTTGACCCTAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCA
GGGGGAATCCATGAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCG
CAAAGAAGGCCATATACATGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTAC
AATACAGCACTGAAGCCAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTCAGCCTCTAC
TAAAGTTGTCATCCGTGGAGCAGGAAA

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FIGURE 107

CGACGCTCTAGCGGTTACCGCTGCGGGCTGGCTGGGCGTAGTGGGGCTGCGCGGCTGCCACG
GAGCTAGAGGGCAAGTGTGCTCGGCCCAGCGTGAGGGAACGCGGGCGGCCAGACAACGGGC
TGGGCTCCGGGGCCTGCGGCGCGGGCGCTGAGCTGGCAGGGCGGGTGGGGCGCGGGCTGCA
TCCGCATCTCCTCCATCGCCTGCAGTAAGGGCGGCCGCGGCGAGCCTTTGAGGGGAACGACT
TGTCGGAGCCCTAACCAGGGGTGTCTCTGAGCCTGGTGGGATCCCCGGAGCGTCACATCACT
TTCCGATCACTTCAAAGTGGTTAAAACTAATATTTATATGACAGAAGAAAAAGATGTCATT
CCGTAAAGTAAACATCATCATCTTGGTCCTGGGCTGTTGCTCTCTTCTTACTGGTTTTGCAC
CATAACTTCCTCAGCTTGAGGCAGTTTGTAAAGGAATGAGGTTACAGATTAGGAATTGTAG
GGCCTCAACCTATAGGACTTTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGA
GGAGATTCCTGTGGTCATCGCTGCATCTGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAA
ACAGCATTCAGCACAACACTCGCTCCAATGTGATTTTCTACATTGTTACTCTCAACAATACA
GCAGACCATCTCCGGTCCTGGGCTCAACAGTGATTCCCTGAAAAGCATCAGATACAAAATTG
TCAATTTTGACCCTAACTTTTGAAGGAAAAGTAAAGGAGGATCCTGACCAGGGGGAATCC
ATGAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGGTTCCAGCGCAAAGAAGG
CCATATACATGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGCA
CTGAAGCCAGGACATGCAGCTGCATTTTTCAGAAGATTGTGATTCAGCCTCTACTAAAGTTGT
CATCCGTGGAGCAGGAAACCAGTACAATTACATTGGCTATCTTGACTATAAAAAGGAAAGAA
TTCGTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTTTTGTGCAAAC
CTGACGGAATGGAAACGACAGAATATACTAACCAACTGGAAAAATGGATGAAACTCAATGT
AGAAGAGGGACTGTATAGCAGAACCCTGGCTGGTAGCATCACAACACCTCCTCTGCTTATCG
TATTTTATCAACAGCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGGTTCCAGT
GCTGGAAAACGATATTACCTCAGTTTGTAAAGGCTGCCAAGTTACTCCATTGGAATGGACA
TTTGAAGCCATGGGGAAGGACTGCTTCATATACTGATGTTTGGGGAAAAATGGTATATTCCA
GACCCAACAGGCAAATTCAACCTAATCCGAAGATATACCGAGATCTCAAACATAAAGTGAAA
CAGAATTTGAACTGTAAGCAAGCATTTCTCAGGAAGTCCTGGAAGATAGCATGCGTGGGAAG
TAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAAGATGTGTCAGCTAG
GTAAAGATGACAACTGCCCTGTCTGGCAGTCAGCTTCCCAGACAGACTATAGACTATAAAT
ATGTCTCCATCTGCCTTACCAAGTGTTCCTTACTACAATGCTGAATGACTGGAAAGAAGAA
CTGATATGGCTAGTTTCACTAGCTGGTACAGATAATTCAAACTGCTGTTGGTTTTAATTTT
GTAACCTGTGGCCTGATCTGTAAATAAACTTACATTTTCAATAGGTAAAAA

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FIGURE 108

CTGCAGGTAGACATCTCCACTGCCCAGGAATCACTGAGCGTGCAGACAGCACAGCCTCCTCT
GAAGGCCGGCCATACCAGAGTCCTGCCTCGGCATGGGCCTCACCATTGAGGCAGCTCCACTG
TCTGTGCTGGTCTGAGGGTGCTGCCTGTCATGGGGGCAGCCATCTCCCAGGGGGCCCTCATC
GCCATCGTCTGCAACGGTCTCGTGGGCTTCTTGCTGCTGCTGCTCTGGGTATCCTCTGCTG
GGCCTGCCATTCTCGTCTGCCGACGTTGACTCTCTCTCTGAATCCAGTCCCAACTCCAGCCC
TGGCCCCCTGTCCTGAGAAGGCCCCACCACCCCAGAAGCCCAGCCATGAAGGCAGCTACCTGC
TGCAGCCCCTGAAGGCCCCCTGGCCTAGCCTGGAGCCCAGGACCTAAGTCCACCTCACCTAGAG
CCTGGAATTAGGATCCCAGAGTTCAGCCAGCCTGGGGTCCAGAACTCAAGAGTCCGCCTGCT
TGGAGCTGGACCCAGCGGCCCAGAGTCTAGCCAGCTTGGCTCCAATAGGAGCTCAGTGGCCC
TAAGGAGATGGGCCTGGGGTGGGGGCTTATGAGTTGGTGCTAGAGCCAGGGCCATCTGGACT
ATGCTCCATCCCAAGGGCCAAGGGTCAGGGGCCGGGTCCACTCTTTCCCTAGGCTGAGCACC
TCTAGGCCCTCTAGGTTGGGGAAGCAAACCTGGAACCCATGGCAATAATAGGAGGGTGTCCAG
GCTGGGCCCCCTCCCCTGGTCCTCCCAGTGTTTGCTGGATAATAAATGGAACCTATGGCTCTAA
AAAAAAAAAAAAAAAAAAAA

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FIGURE 109

MGAAISQGALIAIVCNGLVGFLLLLLWVILCWACHSRLPTLTLSLNPVPTPALAPVLRPHH
PRSPAMKAATCCSPEGPWPSLEPRT

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FIGURE 110

GTTTGAATTCCTTCAACTATACCCACAGTCCAAAAGCAGACTCACTGTGTCCCAGGCTACCA
GTTCTCCAAGCAAGTCATTTCCCTTATTTAACCGATGTGTCCCTCAAACACCTGAGTGCTA
CTCCCTATTTGCATCTGTTTTGATAAATGATGTTGACACCCTCCACCGAATTCTAAGTGGA
TCATGTCGGGAAGAGATACAATCCTTGGCCTGTGTATCCTCGCATTAGCCTTGTCTTTGGCC
ATGATGTTTACCTTCAGATTCATCACCACCCTTCTGGTTCACATTTTCATTTCAATTGGTTAT
TTTGGGATTGTTGTTTGTCTGCGGTGTTTTATGGTGGCTGTATTATGACTATACCAACGACC
TCAGCATAGAATTGGACACAGAAAGGGAAAAATATGAAGTGCGTGCTGGGGTTTGCTATCGTA
TCCACAGGCATCACGGCAGTGCTGCTCGTCTTGATTTTTGTTCTCAGAAAGAGAATAAAATT
GACAGTTGAGCTTTTCCAAATCACAAATAAAGCCATCAGCAGTGCTCCCTTCCTGCTGTTCC
AGCCACTGTGGACATTTGCCATCCTCATTTTCTTCTGGGTCTCTGGGTGGCTGTGCTGCTG
AGCCTGGGAAGTGCAGGAGCTGCCAGGTTATGGAAGGCGGCCAAGTGGAATATAAGCCCCCT
TTCGGGCATTTCGGTACATGTGGTTCGTACCATTTAATTGGCCTCATCTGGACTAGTGAATTCA
TCCTTGCGTGCCAGCAAATGACTATAGCTGGGGCAGTGGTACTTGTTATTTCAACAGAAGT
AAAAATGATCCTCCTGATCATCCCATCCTTTCGTCTCTCTCCATTCTCTTCTTCTACCATCA
AGGAACCGTTGTGAAAGGGTCATTTTTAATCTCTGTGGTGAGGATTCGAGAATCATTGTCA
TGTACATGCAAAACGCACTGAAAGAACAGCAGCATGGTGCATTGTCCAGGTACCTGTTCCGA
TGCTGCTACTGCTGTTTCTGGTGTCTTGACAAATACCTGCTCCATCTCAACCAGAATGCATA
TACTACAAGTCTATTAATGGGACAGATTTCTGTACATCAGCAAAAGATGCATTCAAATCT
TGTTCCAAGAACTCAAGTCACTTTACATCTATTAAGTCTTTGGAGACTTCATAATTTTTCTA
GGAAAGGTGTTAGTGGTGTGTTTCACTGTTTTTGGAGGACTCATGGCTTTTAACTACAATCG
GGCATTCCAGGTGTGGGCAGTCCCTCTGTTATTGGTAGCTTTTTTGCCTACTTAGTAGCCC
ATAGTTTTTTATCTGTGTTTGAAACTGTGCTGGATGCATTTTCTGTGTTTTGCTGTTGAT
CTGGAAACAAATGATGGATCGTCAGAAAAGCCCTACTTTATGGATCAAGAATTTCTGAGTTT
CGTAAAAAGGAGCAACAAATTAAACAATGCAAGGGCACAGCAGGACAAGCACTCATTAAGGA
ATGAGGAGGGAACAGAACTCCAGGCCATTGTGAGATAGATACCCATTTAGGTATCTGTACCT
GGAAACATTTCTTCTAAGAGCCATTTACAGAATAGAAGATGAGACCACTAGAGAAAAGTT
AGTGAATTTTTTTTTTAAAGACCTAATAAACCTATTCTTCCTCAAAA

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FIGURE 111

MSGRDTILGLCILALALSLAMMFTFRFITLLVHIFISLVILGLLFVCGVLWWLYDYTNDL
SIELDTERENMKCVLGFAIVSTGITAVLLVLIFVLRKRIKLTVELFQITNKAISSAPFLLFQ
PLWTFAILIFFWVLWVAVLLSLGTAGAAQVMEGGQVEYKPLSGIRYMWSYHLIGLIWTSEFI
LACQQMTIAGAVVTCYFNRSKNDPPDHPILSSLSILFFYHQGTVVKGSFLISVVRIPRIIVM
YMQNALKEQQHGALSRYLFRCCYCCFWCLDKYLLHLNQNAYTTTAINGTDFCTSAKDAFKIL
SKNSSHFTSINCFGDFIIFLGKVLVVCFTVFGGLMAFNYNRAFQVWAVPLLLVAFFAYLVAH
SFLSVFETVLDALFLCFAVDLETNDGSSEKPYFMDQEFLSFVKRSNKLNNARAQQDKHSLRN
EEGTELQAIVR

[illegible]

FIGURE 113

MRTVVLTMKASVIEMFLVLLVTGVHSNKETAKKIKRPKFTVPQINCDVKAGKIIDPEFIVKC
PAGCQDPKYHVGTDVYASYSSVCGAAVHSGVLDNSGGKILVRKVAGQSGYKGSYSNGVQSL
SLPRWRESFIVLESKPKKGVTPSALTYSKSPAAQAGETTKAYQRPPIPGTTAQPVTLMQ
LLAVTVAVATPTTLPRPSPSAASTTIPRPQSVGHRSEQEMDLWSTATYTTSSQNRPRADPGIQ
RQDPGAAAFQKPVGADVSLGLVPKEELSTQSLEPVSLGDPNCKIDLSFLIDGSTSIGKRRFR
IQKQLLADVAQALDIGPAGPLMGVVQYGDNPATHFNLKTHNTSRDLKTAIEKITQRGGLSNV
GRAISFVTKNFFSKANGNRSGAPNVVVVMVDGWPTDKVEEASRLARESGINIFFITIEGAAE
NEKQYVVEPNFANKAVCRTNGFYSLHVQSWFGLHKTLOPLVKRVCDTDRLACSKTCLNSADI
GFVIDGSSSVGTGNFRTVLQFVTNLTKFEISDTRIGAVQYTYEQRLFGFDKYSSKPD
LNAIKRVGYWSGGTSTGAAINFALEQLFKKSKPNKRKLMILITDGRSYDDVRIPAMAAHLKG
VITYAIGVAWAAQEELEVIATHPARDHSFFVDEFNLHQYVPRIIQNICTEFNSQPRN

FIGURE 114

CAGGATGAACTGGTTGCAGTGGCTGCTGCTGCTGCGGGGCGCTGAGAGGACACGAGCTCTA
TGCCTTTCCGGCTGCTCATCCCGCTCGGCCTCCTGTGCGCGCTGCTGCCTCAGCACCATGGT
GCGCCAGGTCCCAGCGCTCCGCGCCAGATCCCGCCCACTACAGTTTTTCTCTGACTCTAAT
TGATGCACTGGACACCTTGCTGATTTTGGGGAATGTCTCAGAATTCCAAAGAGTGGTTGAAG
TGCTCCAGGACAGCGTGGACTTTGATATTGATGTGAACGCCTCTGTGTTTGAACAAACATT
CGAGTGGTAGGAGGACTCCTGTCTGCTCATCTGCTCTCCAAGAAGGCTGGGGTGGAAGTAGA
GGCTGGATGGCCCTGTTCCGGGCCTCTCCTGAGAATGGCTGAGGAGGCGGCCCGAAAACCTCC
TCCCAGCCTTTTACAGACCCCCACTGGCATGCCATATGGAACAGTGAACCTTACTTCATGGCGTG
AACCAGGAGAGACCCCTGTACCTGTACGGCAGGGATTGGGACCTTCATTGTTGAATTTGC
CACCTTGAGCAGCCTCACTGGTGACCCGGTGTTTGAAGATGTGGCCAGAGTGGCTTTGATGC
GCCTCTGGGAGAGCCGGTCAGATATCGGGCTGGTCGGCAACCACATTGATGTGCTCACTGGC
AAGTGGGTGGCCAGGACGCAGGCATCGGGGCTGGCGTGGACTCCTACTTTGAGTACTTGGT
GAAAGGAGCCATCCTGCTTCAGGATAAGAAGCTCATGGCCATGTTCTTAGAGTATAACAAAG
CCATCCGGAACCTACACCCGCTTCGATGACTGGTACCTGTGGGTTTCAAGTGTACAAGGGGACT
GTGTCCATGCCAGTCTTCCAGTCTTGGAGGCCTACTGGCCTGGTCTTCAGAGCCTCATTTGG
AGACATTGACAATGCCATGAGGACCTTCCTCAACTACTACACTGTATGGAAGCAGTTTGGGG
GGCTCCCGGAATTCTACAACATTCTCAGGGATACACAGTGGAGAAGCGAGAGGGCTACCCA
CTTCGGCCAGAACTTATTGAAAGCGCAATGTACCTCTACCGTGCCACGGGGGATCCCACCT
CCTAGAACTCGGAAGAGATGCTGTGGAATCCATTGAAAAAATCAGCAAGGTGGAGTGGCGAT
TTGCAACAATCAAAGATCTGCGAGACCACAAGCTGGACAACCGCATGGAGTCGTTCTTCTCTG
GCCGAGACTGTGAAATACCTCTACCTCCTGTTTGACCCAACCACTTCATCCACAACAATGG
GTCCACCTTCGACGCGGTGATCACCCCTATGGGGAGTGCATCCTGGGGGCTGGGGGGTACA
TCTTCAACACAGAAGCTCACCCCATCGACCTTGCCGCCCTGCACTGCTGCCAGAGGCTGAAG
GAAGAGCAGTGGGAGGTGGAGGACTTGATGAGGGAATTCTACTCTCTCAAACGGAGCAGGTC
GAAATTTAGAAAAACACTGTTAGTTTCGGGGCCATGGGAACCTCCAGCAAGGCCAGGAACAC
TCTTCTCACCAGAAAACCATGACCAGGCAAGGGAGAGGAAGCCTGCCAAACAGAAGGTCCCA
CTTCTCAGCTGCCCCAGTCAGCCCTTACCTCCAAGTTGGCATTACTGGGACAGGTTTTCTCT
AGACTCCTCATTAACCACTGGATAATTTTTTTATTTTTATTTTTTTGAGGCTAAACTATAATA
AATTGCTTTTGGCTATCATAAAA

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FIGURE 115

MPFRLLIPLGLLCALLPQHHGAPGPDGSAPDPAHYSFSLTLIDALDTLLIILGNVSEFQRVVE
VLQDSVDFDIDVNASVFETNIRVVGGLLSAHLLSKKAGVEVEAGWPCSGPLLMAEEAARKL
LPAFQTPTGMPYGTVNLLHGVNPGETPVTCTAGIGTFIVEFATLSSLTGDPVFEDVARVALM
RLWESRSDIGLVGNHIDVLTGKWVAQDAGIGAGVDSYFEYLVKGAILLQDKKLMAMFLEYNK
AIRNYTRFDDWYLVVQMYKGTVSMPVFQSLEAYWGLQSLIGDIDNAMRTFLNYYTVWKQFG
GLPEFYNI PQGYTVEKREGYPLRPELIESAMYLYRATGDPTLLELGRDAVESIEKISKVECG
FATIKDLRDHKLDNRMESFFLAETVKYLYLLFDPTNFIHNNGSTFDAVITPYGECILGAGGY
IFNTEAHPIDLAALHCCQRLKEEQWEVEDLMREFYSLKRSRSKFQKNTVSSGPWEPPARPGT
LFSPENHDQARERKPAKQKVPLLSCPSQPFTSKLALLGQVFLDSS

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FIGURE 116

AAAGTTACATTTTCTCTGGAACCTCCTAGGCCACTCCCTGCTGATGCAACATCTGGGTTTG
GGCAGAAAGGAGGGTGCTTCGGAGCCCGCCCTTTCTGAGCTTCCTGGGCCGGCTCTAGAACA
ATTCAGGCTTCGCTGCGACTCAGACCTCAGCTCCAACATATGCATTCTGAAGAAAGATGGCT
GAGATGGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCAAACCTGAGTCTACCA
AAATGCAGACTTTTACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTCATGTGGTTTTTCT
ACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGCCTGCCCCCTCAGAACCTC
TCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTGATCGCGCCTGGAGA
AACAGTGTACTATTCTGTGCAATACCAGGGGGAGTACGAGAGCCTGTACACGAGCCACATCT
GGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGTGATGTCACTGATGACATC
ACGGCCACTGTGCCATACAACCTTCGTGTGAGGGCCACATTGGGCTCACAGACCTCAGCCTG
GAGCATCCTGAAGCATCCCTTTAATAGAACTCAACCATCCTTACCCGACCTGGGATGGAGA
TCACCAAAGATGGCTTCACCTGGTTATTGAGCTGGAGGACCTGGGGCCCCAGTTTGAGTTC
CTTGTGGCCTACTGGAGGAGGGAGCCTGGTGCCGAGGAACATGTCAAATGGTGAGGAGTGG
GGGTATTCCAGTGCACCTAGAAACCATGGAGCCAGGGGCTGCATACTGTGTGAAGGCCCAGA
CATTCGTGAAGGCCATTGGGAGGTACAGCGCCTTCAGCCAGACAGAATGTGTGGAGGTGCAA
GGAGAGGCCATTCCCCTGGTACTGGCCCTGTTTGCCTTTGTTGGCTTCATGCTGATCCTTGT
GGTCGTGCCACTGTTCTGTGGAATAAGGGCCGGCTGCTCCAGTACTCCTGTTGCCCGTGG
TGGTCTCCAGACACCTTGAAAATAACCAATTACCCCAAGTAATCAGCTGCAGAAGG
GAGGAGGTGGATGCCTGTGCCACGGCTGTGATGTCTCCTGAGGAACCTCCTCAGGGCCTGGAT
CTCATAGSTTTGCGGAAGGGCCCAGGTGAAGCCGAGAACCTGGTCTGCATGACATGGAAACC
ATGAGGGGACAAGTTGTGTTTTCTGTTTTCCGCCACGGACAAGGGATGAGAGAAGTAGGAAGA
GCCTGTTGTCTACAAGTCTAGAAGCAACCATCAGAGGCAGGGTGGTTTGTCTAACAGAACAC
TGACTGAGGCTTAGGGGATGTGACCTCTAGACTGGGGGCTGCCACTTGCTGGCTGAGCAACC
CTGGGAAAAGTGACTTCATCCCTTCGGTCCTAAGTTTTCTCATCTGTAATGGGGGAATTACC
TACACACCTGCTAAACACACACACACAGAGTCTCTCTATATATACACACGTACACATAAA
TACACCCAGCACTTGCAAGGCTAGAGGGAACTGGTGACACTCTACAGTCTGACTGATTGAG
TGTTTCTGGAGAGCAGGACATAAATGTATGATGAGAATGATCAAGGACTCTACACACTGGGT
GGCTTGAGAGCCCACTTTCCCAGAATAATCCTTGAGAGAAAAGGAATCATGGGAGCAATGG
TGTTGAGTTCACCTCAAGCCCAATGCCGGTGAGAGGGGAATGGCTTAGCGAGCTCTACAGT
AGGTGACCTGGAGGAAGGTCACAGCCACACTGAAAATGGGATGTGCATGAACACGGAGGATC
CATGAACTACTGTAAAGTGTGACAGTGTGTGCACACTGCAGACAGCAGGTGAAATGTATGT
GTGCAATGCGACGAGAATGCAGAAGTCAGTAACATGTGCATGTTTGTGTGCTCCTTTTTTTC
TGTTGGTAAAGTACAGAATTCAGCAAATAAAAAGGGCCACCCTGGCCAAAAGCGGTAAAAAA
AAAAAAAAA

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FIGURE 117

MQTFTMVLEEIWTSFLMWFFYALIPCLLTDEVAILPAPQNLSVLSTNMKHLMLWSPVIAPGE
TVYYSVEYQGEYESLYTSHIWIPSSWCSLTEGPECDVTDDITATVPYNLRVRATLGSQTS
SILKHPFNRNSTILTRPGMEITKDGFLVIELEDLGPQFEFLVAYWRREPGAEEHVKMVRSG
GIPVHLETMEPGAAYCVKAQTFVKAIGRYSAFSQTECVEVQGEAIPLVLALFAFVGFMLILV
VVPLFVWKMGRLLQYSCCPVVVLPDTLKITNSPQKLISCRREEVDACATAVMSPEELLRAWIS

Important features:**Signal peptide:**

amino acids 1-29

Transmembrane domain:

amino acids 230-255

N-glycosylation sites.

amino acids 40-43 and 134-137

Tissue factor proteins homology.

amino acids 92-119

Integrins alpha chain protein homology.

amino acids 232-262

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FIGURE 118

TCCTGCTGATGCACATCTGGGTTTGGCAAAGGAGGTTGCTTCGAGCCGCCCTTTCTAGCTT
CCTGGCCGGCTCTAGAACAATT CAGGCTTCGCTGCGACTAGACCTCAGCTCCAACATATGCA
TTCTGAAGAAAGATGGCTGAGATGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGG
TCAAAC TGAGTCTACCAAATGCAGACTTTT CACAATGGTTCTAGAAGAAATCTGGACAAGTCT
TTTCATGTGGTTTTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGC
CTGCCCCCTCAGAACCTCTCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCA
GTGATCGCGCCTGGAGAAACAGTGTACTATTCTGTCTGAATACCAGGGGGAGTACGAGAGCCT
GTACACGAGCCACATCTGGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGTG
ATGTCACTGATGACATCACGGCCACTGTGCCATACAACCTTTGTGT CAGGGCCACATTGGGC
TCACAGACCTCAGCCTGGAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATCCTTAC
CCGACCTGGGATGGAGATCACCAAAGATGGCTTNCACCTGGTTATTGAGCTGGAGGACCTGG
GGCCCCAGTTTGAGTTCCTTGTTGGCCTANTGGAGGAGGGGGCGAACCCCTTGCGGCGCAAGGG
GTTNGCGAACCCCTTGCGGCCGCTGGGGTATCTCTCGAGAAAAGAGAGGCCCAATATGACCCAC
ATACTCAATATGGACGAANTGCTATTGTCCACCTGTTTGAGTGGCGCTGGGTTGAT

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FIGURE 119

CGGACGCGTGGGCCGCCACCTCCGGAACAAGCCATGGTGGCGGCGACGGTGGCAGCGGCGTG
GCTGCTCCTGTGGGCTGCGGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAGGCGG
TCAACATCCGGGGCAAAC TGGTGTGCTGGAGAAGTACCGCGGATCGGTGTCCCTGGTGGTG
AATGTGGCCAGCGAGTGCGGCTTACAGACCAGCACTACCGAGCCCTGCAGCAGCTGCAGCG
AGACCTGGGCCCCCACCCTTTAACGTGCTCGCCTTCCCCTGCAACCAGTTTGGCCAACAGG
AGCCTGACAGCAACAAGGAGATTGAGAGCTTTGCCCGCCGCACCTACAGTGTCTCATTCCCC
ATGTTTAGCAAGATTGCAGTCACCGGTACTGGTGCCCATCCTGCCTTCAAGTACCTGGCCCA
GACTTCTGGGAAGGAGCCACCTGGAACCTTCTGGAAGTACCTAGTAGCCCCAGATGGAAAGG
TGGTAGGGGCTTGGGACCCAACTGTGTGTCAGTGGAGGAGGTCAGACCCAGATCACAGCGCTC
GTGAGGAAGCTCATCCTACTGAAGCGAGAAGACTTATTAACCACCGCGTCTCCTCCTCCACCA
CCTCATCCCGCCCACCTGTGTGGGGCTGACCAATGCAAAC TCAAATGGTGCTTCAAAGGGAG
AGACCCACTGACTCTCCTTCCTTTACTCTTATGCCATTGGTCCCATCATTCTTGTGGGGGAA
AAATTCTAGTATTTTGATTATTTGAATCTTACAGCAACAAATAGGAACTCCTGGCCAATGAG
AGCTCTTGACCAGTGAATCACCAGCCGATACGAACGTCTTGCCAACAAAAATGTGTGGCAAA
TAGAAGTATATCAAGCAATAATCTCCACCCAAGGCTTCTGTAAACTGGGACCAATGATTAC
CTCATAGGGCTGTTGTGAGGATTAGGATGAAATACCTGTGAAAGTGCCTAGGCAGTGCCAGC
CAAATAGGAGGCATTCAATGAACATTTTTTGCATATAAACCAAAAAATAACTTGTTATCAAT
AAAAACTTGCAATCCAACATGAATTTCCAGCCGATGATAATCCAGGCCAAAGGTTTAGTTGTT
GTTATTTCTCTGTATTATTTTCTTCATTACAAAAGAAATGCAAGTTCATTGTAACAATCCA
AACAAATACCTCACGATATAAAATAAAAATGAAAGTATCCTCCTCAAAAA

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FIGURE 120

MVAATVAAAWLLLWAAACAQQEQDFYDFKAVNIRGKLVSLEKYRGSVSLVVNVASECGFTDQ
HYRALQQQLQRD LGPHHFNVLAFFPCNQFGQQEPDSNKEIESFARRTYSVSFPMFSKIAVTGTG
AHPAFKYLAQTSGKEPTWNFWKYL VAPDGKVVGAWDPTVSVEEVRPQITALVRKLILLKREDL

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FIGURE 121

CGGACGCGTGGGCGGGCCGGGACGCAGGGCAAAGCGAGCCATGGCTGTCTACGTCGGGATGC
TGCGCCTGGGGAGGCTGTGCGCCGGGAGCTCGGGGGTGCTGGGGGCCCGGGCCGCCCTCTCT
CGGAGTTGGCAGGAAGCCAGGTTGCAGGGTGTCGCTTCCTCAGTTCAGAGAGGTGGATCG
CATGGTCTCCACGCCCATCGGAGGCCTCAGCTACGTTAGGGGTGCACCAAAAAGCATCTTA
ACAGCAAGACTGTGGGCCAGTGCCCTGGAGACCACAGCACAGAGGGTCCCAGAACGAGAGGCC
TTGGTCGTCTCCATGAAGACGTCAGGTTGACCTTTGCCCAACTCAAGGAGGAGGTGGACAA
AGCTGCTTCTGGCCTCCTGAGCATTGGCCTCTGCAAAGGTGACCGGCTGGGCATGTGGGGAC
CTAACTCCTATGCATGGGTGCTCATGCAGTTGGCCACCGCCCAGGCGGGCATCATTCTGGTG
TCTGTGAACCCAGCCTACCAGGCTATGGAAGTGGAGTATGTCCTCAAGAAGGTGGGCTGCAA
GGCCCTTGTGTTCCCCAAGCAATTCAAGACCCAGCAATACTACAACGTCCTGAAGCAGATCT
GTCCAGAAGTGGAGAATGCCCAGCCAGGGGCTTGAAGAGTCAGAGGCTCCCAGATCTGACC
ACAGTCATCTCGGTGGATGCCCCCTTTGCCGGGGACCTGCTCCTGGATGAAGTGGTGGCGGC
TGGCAGCACACGGCAGCATCTGGACCAGCTCCAATAACAACAGCAGTTCCTGTCTGCCATG
ACCCCATCAACATCCAGTTCACCTCGGGGACAACAGGCAGCCCCAAGGGGGCCACCTCTCC
CACTACAACATTGTCAACAACCTCCAACATTTTAGGAGAGCGCCTGAAACTGCATGAGAAGAC
ACCAGAGCAGTTGCGGATGATCCTGCCCAACCCCTGTACCATTGCCTGGGTTCGGTGGCAG
GCACAATGATGTGTCTGATGTACGGTGCCACCCTCATCCTGGCCTCTCCCATCTTCAATGGC
AAGAAGGCACTGGAGGCCATCAGCAGAGAGAGAGGCACCTTCCTGTATGGTACCCCCACGAT
GTTCTGTGGACATTCTGAACCAGCCAGACTTCTCCAGTTATGACATCTCGACCATGTGTGGAG
GTGTCAATTGCTGGGTCCCCTGCACCTCCAGAGTTGATCCGAGCCATCATCAACAAGATAAAT
ATGAAGGACCTGGTGGTTGCTTATGGAACCACAGAGAACAGTCCCGTGACATTCGCGCACTT
CCCTGAGGACACTGTGGAGCAGAAGGCAGAAAGCGTGGGCAGAATTATGCCTCACACGGAGG
CCCGGATCATGAACATGGAGGCAGGGACGCTGGCAAAGCTGAACACGCCCCGGGGAGCTGTGC
ATCCGAGGGTACTGCGTCATGCTGGGCTACTGGGGTGAGCCTCAGAAGACAGAGGAAGCAGT
GGATCAGGACAAGTGGTATTGGACAGGAGATGTGCCACAATGAATGAGCAGGGCTTCTGCA
AGATCGTGGGCCGCTCTAAGGATATGATCATCCGGGGTGGTGAGAACATCTACCCCGCAGAG
CTCGAGGACTTCTTTACACACACCCGAAGGTGCAGGAAGTGCAGGTGGTGGGAGTGAAGGA
CGATCGGATGGGGGAAGAGATTTGTGCTGCATTCCGCTGAAGGACGGGGAGGAGACCACGG
TGGAGGAGATAAAAGCTTTCTGCAAAGGGAAGATCTCTCACTTCAAGATTCCGAAGTACATC
GTGTTTGTCAAACTACCCCTCACCATTTCAGGAAAGATCCAGAAATTCAAATTCGAGA
GCAGATGGAACGACATCTAAATCTGTGAATAAAGCAGCAGGCCTGTCTGGCCGGTTGGCTT
GACTCTCTCCTGTCAGAATGCAACCTGGCTTTATGCACCTAGATGTCCCCAGCACCCAGTTC
TGAGCCAGGCACATCAAATGTCAAGGAATTGACTGAACGAACTAAGAGCTCCTGGATGGGTC
CGGGAACCTCGCCTGGGCACAAGGTGCCAAAAGGCAGGCAGCCTGCCAGGCCCTCCCTCCTG
TCCATCCCCCACATTCCCCTGTCTGTCTTGTGATTGTCATAAAGAGCTTCTGTTTTCTTT
GAAAAAAAAAAAAAAAAA

FIGURE 122

MAVYVGMLRLGRLCAGSSGVLGARAALSRWQEARLQGVRFLSSREVD RMVSTPIGGLSYVQ
GCTKKHLNSKTVGQCLETTAQRVPEREALVVLHEDVRLTFAQLKEEVDKAASGLLSIGLCKG
DRLGMWGPNSYAWVLMQLATAQAGIILVSVNPAYQAMELEYVLKKVGCKALVFPKQFKTQQY
YNVLKQICPEVENAQP GALKSQRLPDLTTVISVDAPLP GTLLLDEVVAAGSTRQHLDQLQYN
QQFLSCHDPINIQFTSGTTGSPKGATLSHYNIVNNSNILGERLKLHEKTPEQLRMILPNPLY
HCLGSVAGTMMCLMYGATLILASPIFNGKKALEAISRERGTFLYGTPTMFVDILNQPDFSSY
DISTMCGGVIAGSPAPPELIRAIINKINMKDLVVAYGTTENSPVTF AHFPEDTVEQKAESVG
RIMPHTEARIMNMEAGTLAKLNTPGELCIRGYCVMLGYWGEPQKTEEAVDQDKWYWTGDVAT
MNEQGFCKIVGRSKDMIIRGGENIYPAELEDFHHTHPKVQEVQVVGKDDRMGEEICACIRL
KDGEETTVEEIKAFCKGKISHFKIPKYIVFVTNYPLTISGKIQKFKLREQMERHLNL

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FIGURE 123

CAACTCCAACATTTTAGGAGAGCGCCTGAAACTGCATGAGAAGACACCAGAGCAGTTGCGGA
TGATCCTGCCCCAACCCCTGTACCATTGCCTGGGTTCCGTGGCAGGCACAATGATGTGTCTG
ATGTACGGTGCCACCCTCATCCTGGCCTCTCCCATCTTCAATGGCAAGAAGGCACTGGAGGC
CATCAGCAGAGAGAGAGGCACCTTCCTGTATGGTACCCCCACGATGTTTCGTGGACATTCTGA
ACCAGCCAGACTTCTCCAGTTATGACATCTCGACCATGTGTGGAGGTGTCATTGCTGGGTCC
CCTGCACCTCCAGAGTTGATCCGAGCCATCATCAACAAGATAAATATGAAGGACCTGGTGGT
TGCTTATGGAACCACAGAGAACAGTCCCGTGACATTCGCGCACTTCCCTGAGGACACTGTGG
AGCAGAAGGCAGAAAGCGTGGGCAGAATTATGCCTCACACGGAGGCGCGGATCATGAACATG
GAGGCAGGGACGCTGGCAAAGCTGAACACGCCCGGGGAGCTGTGCATCCGAGGGTACTGCGT
CATGCTGGGCTACTGGGGTGAGCCTCAGAAGACAGAGGAAGCAGTGGATCAGGACAAGTGGT
ATTGGACAGGAGATGTCGCCAC

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FIGURE 124

GAGCAGGACGGAGCCATGGACCCCGCCAGGAAAGCAGGTGCCCAGGCCATGATCTGGACTGC
AGGCTGGCTGCTGCTGCTGCTGCTTCGCGGAGGAGCGCAGGCCCTGGAGTGCTACAGCTGCG
TGCAGAAAGCAGATGACGGATGCTCCCCGAACAAGATGAAGACAGTGAAGTGCGCGCCGGGC
GTGGACGTCTGCACCGAGGCCGTGGGGGCGGTGGAGACCATCCACGGACAATTCTCGCTGGC
AGTGCGGGGTTGCGGTTCTGGGACTCCCCGGCAAGAATGACCGCGGCCTGGATCTTCACGGGC
TTCTGGCGTTTCATCCAGCTGCAGCAATGCGCTCAGGATCGCTGCAACGCCAAGCTCAACCTC
ACCTCGCGGGCGCTCGACCCGGCAGGTAATGAGAGTGCATACCCGCCCAACGGCGTGGAGTG
CTACAGCTGTGTGGGCCTGAGCCGGGAGGCGTGCCAGGGTACATCGCCGCCGGTCTGTGAGCT
GCTACAACGCCAGCGATCATGTCTACAAGGGCTGCTTCGACGGCAACGTCACCTTGACGGCA
GCTAATGTGACTGTGTCTTGCCTGTCCGGGGCTGTGTCCAGGATGAATTCTGCACTCGGGA
TGGAGTAACAGGCCCAGGGTTCACGCTCAGTGGCTCCTGTTGCCAGGGGTCCCGCTGTAACT
CTGACCTCCGCAACAAGACCTACTTCTCCCCTCGAATCCCAACCCTTGTCGGGCTGCCCCCT
CCAGAGCCCACGACTGTGGCCTCAACCACATCTGTCACCACTTCTACCTCGGCCCCAGTGAG
ACCCACATCCACCACCAAACCCATGCCAGCGCCAACCAAGTCAGACTCCGAGACAGGGAGTAG
AACACGAGGCCTCCCGGGATGAGGAGCCCAGGTTGACTGGAGGCGCCGCTGGCCACCAGGAC
CGCAGCAATTCAGGGCAGTATCCTGCAAAAGGGGGGCCCCAGCAGCCCCATAATAAAGGCTG
TGTGGCTCCACAGCTGGATTGGCAGCCCTTCTGTTGGCCGTGGCTGCTGGTGTCTTACTGTG
GAGCTTCTCCACCTGGAAATTTCCCTCTCACCTACTTCTCTGGCCCTGGGTACCCCTCTTCT
CATCACTTCTGTTCCCACTGACTGGGCTGGCCAGCCCCTGTTTTTCCAACATTCCC
CAGTATCCCCAGCTTCTGCTGCGCTGGTTTTCGGCTTTGGGAAATAAAATACCGTTGTATAT
ATTCTGCCAGGGGTGTTCTAGCTTTTTGAGGACAGCTCCTGTATCCTTCTCATCTTGTCTC
TCCGCTTGTCTCTTGTGATGTTAGGACAGAGTGAGAGAAGTCAGCTGTCACGGGGAAGGTG
AGAGAGAGGATGCTAAGCTTCCTACTCACTTCTCCTAGCCAGCCTGGACTTTGGAGCGTGG
GGTGGGTGGGACAATGGCTCCCCACTCTAAGCACTGCCTCCCCTACTCCCCGCATCTTTGGG
GAATCGGTTCCCCATATGTCTTCCTTACTAGACTGTGAGCTCCTCGAGGGGGGGCCCGGTAC
CCAATTCGCCCTATAGTGAGTCGTA

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FIGURE 125

MDPARKAGAQAMIWTAGWLLLLLLRGGAQALECYSCVQKADDGCSPNKMKTVCAPGVDVCT
EAVGAVETIHGQFSLAVRGCGSGLPGKNDRGLDLHGLLAFIQLQQCAQDRCNALNLTSRAL
DPAGNESAYPPNGVECYSCVGLSREACQGTSPFVSCYNASDHVYKGCDFGNVTLTAANVTV
SLPVRGCVQDEFCTRDGVTGPGFTLSGSCCQGSRCNSDLRNKTYFSPRIPLVRLPPPEPTT
VASTTSVTTSTSAFVRPTSTTKPMPAPTSQTPRQGEHEASRDEEPRLTGGAAGHQDRSNSG
QYPAKGGPQQPHNKGCVAPTAGLAALLLAVAAGVLL

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FIGURE 127

MELVLVFLCSLLAPMVLASAAEKEKEMDPFHYDYQTLRIGGLVFAVVLFSVGILLILSRCK
CSFNQKPAPGDEEAQVENLITANATEPQKQRTQEVQPSGSLWNLRRLLLEPLDANVDA

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FIGURE 128

AAACTTGACGCCATGAAGATCCCGGTCTTCCTGCCGTGGTGCTCCTCTCCCTCCTGGTGCT
CCTCTGCCCAGGGAGCCACCCTGGGTGGTCCTGAGGAAGAAAGCACCATTGAGAATTATG
CGTCACGACCCGAGGCCTTTAACACCCCGTTCCTGAACATCGACAAATTGCGATCTGCGTTT
AAGGCTGATGAGTTCCTGAACTGGCACGCCCTCTTTGAGTCTATCAAAAGGAACTTCCTTT
CCTCAACTGGGATGCCTTTCTAAGCTGAAAGGACTGAGGAGCGCAACTCCTGATGCCCAGT
GACCATGACCTCCACTGGAAGAGGGGGCTAGCGTGAGCGCTGATTCTCAACCTACCATAACT
CTTTCCTGCCTCAGGAACTCCAATAAAACATTTTCATCCAAA

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FIGURE 129

MKIPVLPVAVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSFAKDE
FLNWHALFESIKRKLPFLNWDAFPKLKGLRSATPDAQ

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FIGURE 130

CAGTTCTGAAATCAATGGAGTTAATTTAGGGAATACAAACCAGCCATGGGGGTGGAGATTGC
CTTTGCCTCAGTGATTCTCACCTGCCTCTCCCTTCTGGCAGCAGGAGTCTCCCAGGTTGTTC
TTCTCCAGCCAGTTCCAACCTCAGGAGACAGGTCCCAAGGCCATGGGAGATCTCTCCTGTGGC
TTTGCCGGCCACTCATGAGAGTGTTTTTGTGTAAAGTATTTTTTAGAATACTGTTGACTTCT
TCATGATTTAATAACCATCCTTTGCGAAGTTTTATGAGGCTTTAGGGGAATGTCAACCCTCA
AATTTTTGTTATACTAGATGGCTTCCATTTACCCACCACTATTTTAAGGTCCCTTTATTTTT
AGGTTCAAGGTTCAATTTGACTTGAGAAAGTGCCCTTCTGCAGCTTCATTGATTTTGTATTATC
TTCACTATTAATTGTAACGATTAAAAAGAATAAGAGCACGCAGACCTCTAGGAGAATATTT
TATCCCTGGGTGCCCCTGACACATTTATGTAGTGATCCCACAAATGTGATTGTTAATTTAAA
TGTTATTCTAATATTAGTACATTCAGTTGTGATGTAATATGAATAACCAGAATCTATTTCTT
AAAAGTTTTGAGTATATTTTTCAACTAGATATTTGTATAGAAAGACTGAATAGTGATG

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FIGURE 131

MGVEIAFASVILTCLSLAAGVSQVLLQPVPTQETGPKAMGDLSCGFAGHS

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FIGURE 132

GGGGAATCTGCAGTAGGTCTGCCGGCGATGGAGTGGTGGGCTAGCTCGCCGCTTCGGCTCTG
GCTGCTGTTGTTCTCCTGCCCTCAGCGCAGGGCCGCCAGAAGGAGTCAGGTTCAAAATGGA
AAGTATTTATTGACCAAATTAACAGGTCTTTGGAGAATTACGAACCATGTTCAAGTCAAAAC
TGCAGCTGCTACCATGGTGTATAGAAGAGGATCTAACTCCTTTCCGAGGAGGCATCTCCAG
GAAGATGATGGCAGAGGTAGTCAGACGGAAGCTAGGGACCCACTATCAGATCACTAAGAACA
GACTGTACCGGGAAAATGACTGCATGTTCCCCTCAAGGTGTAGTGGTGTGAGCACTTTATT
TTGGAAGTGATCGGGCGTCTCCCTGACATGGAGATGGTGATCAATGTACGAGATTATCCTCA
GGTTCCTAAATGGATGGAGCCTGCCATCCCAGTCTTCTCCTTCAGTAAGACATCAGAGTACC
ATGATATCATGTATCCTGCTTGGACATTTTGGGAAGGGGACCTGCTGTTTGGCCAATTTAT
CCTACAGGTCTTGGACGGTGGGACCTCTTCAGAGAAGATCTGGTAAGGTCAGCAGCACAGTG
GCCATGGAAAAAGAAAACTCTACAGCATATTTCCGAGGATCAAGGACAAGTCCAGAACGAG
ATCCTCTCATTCTTCTGTCTCGGAAAAACCCAAAACCTTGTTGATGCAGAATACACCAAAAAC
CAGGCCTGGAAATCTATGAAAGATACCTTAGGAAAGCCAGCTGCTAAGGATGTCCATCTTGT
GGATCACTGCAAATACAAGTATCTGTTTAATTTTCGAGGCGTAGCTGCAAGTTTCCGGTTTA
AACACCTCTTCCTGTGTGGCTCACTTGTTTTCCATGTTGGTGATGAGTGGCTAGAATTCTTC
TATCCACAGCTGAAGCCATGGGTCACTATATCCCAGTCAAACAGATCTCTCCAATGTCCA
AGAGCTGTTACAATTTGTAAAAGCAAATGATGATGTAGCTCAAGAGATTGCTGAAAGGGGAA
GCCAGTTTATTAGGAACCATTTGCAGATGGATGACATCACCTGTTACTGGGAGAACCTCTTG
AGTGAATACTCTAAATTCCTGTCTTATAATGTAACGAGAAGGAAAGGTTATGATCAAATTAT
TCCCCAAATGTTGAAAACCTGAACTATAGTAGTCATCATAGGACCATAGTCCTCTTTGTGGCA
ACAGATCTCAGATATCCTACGGTGAGAAGCTTACCATAAGCTTGGCTCCTATACCTTGAATA
TCTGCTATCAAGCCAAATACCTGGTTTTCTTATCATGCTGCACCCAGAGCAACTCTTGAGA
AAGATTTAAATGTGTCTAATACTGATATGAAGCAGTTCAACTTTTTTGATGAATAAGGA
CCAGAAATCGTGAGATGTGGATTTTGAACCCAACCTCTACCTTTCATTTTCTTAAGACCAATC
ACAGCTTGTGCCTCAGATCATCCACCTGTGTGAGTCCATCACTGTGAAATTGACTGTGTCCA
TGTGATGATGCCCTTTGTCCATTATTTGGAGCAGAAAATTCGTCAATTTGGAAGTAGTACAA
CTCATGTGCTGGAATTGTGAAATTATTCAAGGCGTGATCTCTGTCACTTTATTTTAATGTAGG
AAACCCTATGGGGTTTATGAAAAATACTTGGGGATCATTCTCTGAATGGTCTAAGGAAGCGG
TAGCCATGCCATGCAATGATGTAGGAGTTCTCTTTTGTAAAACCATAAACTCTGTTACTCAG
GAGGTTTCTATAATGCCACATAGAAAGAGGCCAATTGCATGAGTAATTATTGCAATTGGATT
TCAGGTTCCCTTTTTGTGCCTTCATGCCCTACTTCTTAATGCCTCTCTAAAGCCAAA

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FIGURE 133

MEWWASSPLRLWLLLFLLP
SAQGRQKESGSKWKVFI
DQINRSLENYEPCSSQNC
SCYHGVIE
EDLTPFRGGISRKMMAEV
VRRKLGTHYQITKNRLY
REND CMFP
SRCSGVEHFILEVIGRLPD
MEMVINVRDYPQVPKWME
PAIPVFSFSKTSEYHDI
MYPAWTFWEGGPAVWPI
YPTGLGRWDL
FREDLVRSAQWPWKKKN
STAYFRGSRTSPERDPL
ILLSRKNPKLVDAEYTK
NQAWKSMKDT
LGKPAAKDVHLVDHCKY
KYLNFNFRGVAASFRFK
HLFLCGSLVFHVGDEWLE
FFYPQLKPWVH
YIPVKTDLSNVQELLQF
VKANDDVAQEIAERGSQ
FIRNHLQMDDITCYWEN
LLSEYSKFLSY
NVTRRKG YDQII PKML
KTEL

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FIGURE 134

CACCCCTCCATTTCTCGCCATGCCCCCTGCACTGCTCCTGATCCCTGCTGCCCTCGCCTCTT
TCATCCTGGCCTTTGGCACCGGAGTGGAGTTCGTGCGCTTTACCTCCCTTCGGCCACTTCTT
GGAGGGATCCCGGAGTCTGGTGGTCCGGATGCCCCGCCAGGGATGGCTGGCTGCCCTGCAGGA
CCGCAGCATCCTTGCCCCCTGGCATGGGATCTGGGGCTCCTGCTTCTATTTGTTGGGCAGC
ACAGCCTCATGGCAGCTGAAAGAGTGAAGGCATGGACATCCCGGTACTTTGGGGTCCCTCAG
AGGTCACTGTATGTGGCCTGCACTGCCCTGGCCTTGACAGCTGGTGATGCGGTACTGGGAGCC
CATACCCAAAGGCCCTGTGTTGTGGGAGGCTCGGGCTGAGCCATGGGCCACCTGGGTGCCGC
TCCTCTGCTTTGTGCTCCATGTCATCTCCTGGCTCCTCATCTTTAGCATCCTTCTCGTCTTT
GACTATGCTGAGCTCATGGGCCTCAAACAGGTATACTACCATGTGCTGGGGCTGGGCGAGCC
TCTGGCCCTGAAGTCTCCCCGGGCTCTCAGACTCTTCTCCACCTGCGCCACCCAGTGTGTG
TGGAGCTGCTGACAGTGCTGTGGGTGGTGCCTACCCTGGGCACGGACCGTCTCCTCCTTGCT
TTCCTCCTTACCCTCTACCTGGGCCTGGCTCACGGGCTTGATCAGCAAGACCTCCGCTACCT
CCGGGCCCAGCTACAAAGAAAACCTCCACCTGCTCTCTCGGCCCCAGGATGGGGAGGCAGAGT
GAGGAGCTCACTCTGGTTACAAGCCCTGTTCTTCCTCTCCCACTGAATTCTAAATCCTTAAC
ATCCAGGCCCTGGCTGCTTCATGCCAGAGGCCCAAATCCATGGACTGAAGGAGATGCCCCCTT
CTACTACTTGAGACTTTATTCTCTGGGTCCAGCTCCATACCCTAAATTCTGAGTTTCAGCCA
CTGAACTCCAAGGTCCACTTCTCACCAGCAAGGAAGAGTGGGGTATGGAAGTCATCTGTCCC
TTCACTGTTTAGAGCATGACACTCTCCCCCTCAACAGCCTCCTGAGAAGGAAAGGATCTGCC
CTGACCACTCCCCTGGCACTGTTACTTGCCCTCTGCGCCTCAGGGGTCCCCTTCTGCACCGCT
GGCTTCCACTCCAAGAAGGTGGACCAGGGTCTGCAAGTTCAACGGTCATAGCTGTCCCTCCA
GGCCCCAACCTTGCCCTCACCCTCCCGGCCCTAGTCTCTGCACCTCCTTAGGCCCTGCCTCT
GGGCTCAGACCCCAACCTAGTCAAGGGGATTCTCCTGCTCTTAACTCGATGACTTGGGGCTC
CCTGCTCTCCCGAGGAAGATGCTCTGCAGGAAAATAAAAGTCAGCCTTTTTCTAAAAAAA

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FIGURE 135

MAPALLLIPAALASFILAFGTGVEFVRFTSLRPLLGGIPESGGPDARQGWLAALQDRSILAP
LAWDLGLLLLFVGQHSLMAAERVKAWTSRYFGVLQRSLYVACTALALQLVMRYWEPIPKGPV
LWEARAEPWATWVPLLCFVLHVISWLLIFSILLVFDYAELMGLKQVYYHVLGLGEPLALKSP
RALRLFSLRHPVCVELLTVLWVVPTLGTDRLLLAFLLTLYLGLAHGLDQQDLRYLRAQLQR
KLHLLSRPQDGEAE

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FIGURE 136

CCGAGCACAGGAGATTGCCTGCGTTTAGGAGGTGGCTGCGTTGTGGGAAAAGCTATCAAGGA
AGAAATTGCCAAACCATGTCTTTTTTCTGTTTCAGAGTAGTTCACAACAGATCTGAGTGT
TTTAATTAAGCATGGAATACAGAAAACAACAAAAAACTTAAGCTTTAATTTTCATCTGGAATT
CCACAGTTTTCTTAGCTCCCTGGACCCGGTTGACCTGTTGGCTCTTCCCGCTGGCTGCTCTA
TCACGTGGTGCTCTCCGACTACTCACCCGAGTGTAAGAACCTTCGGCTCGCGTGCTTCTG
AGCTGCTGTGGATGGCCTCGGCTCTCTGGACTGTCCTTCCGAGTAGGATGTCACTGAGATCC
CTCAAATGGAGCCTCCTGCTGCTGTCACTCCTGAGTTTCTTTGTGATGTGGTACCTCAGCCT
TCCCCACTACAATGTGATAGAACGCGTGAACCTGGATGTACTTCTATGAGTATGAGCCGATTT
ACAGACAAGACTTTCACTTCACACTTCGAGAGCATTCAAACCTGCTCTCATCAAATCCATTT
CTGGTCATTCTGGTGACCTCCCACCCTTCAGATGTGAAAGCCAGGCAGGCCATTAGAGTTAC
TTGGGGTGAAAAAAGTCTTGGTGGGGATATGAGGTTCTTACATTTTTCTTATTAGGCCAAG
AGGCTGAAAAGGAAGACAAAATGTTGGCATGTCCCTAGAGGATGAACACCTTCTTTATGGT
GACATAATCCGACAAGATTTTTTAGACACATATAATAACCTGACCTTGAAAACCATATGGC
ATTCAGGTGGGTAACCTGAGTTTTGCCCAATGCCAAGTACGTAATGAAGACAGACACTGATG
TTTTCATCAATACTGGCAATTTAGTGAAGTATCTTTTAAACCTAAACCACTCAGAGAAGTTT
TTCACAGGTTATCCTCTAATTGATAATTATTCCTATAGAGGATTTTACCAAAAACCCATAT
TTCTTACCAGGAGTATCCTTTCAAGGTGTTCCCTCCATACTGCAGTGGGTGGGTTATATAA
TGTCCAGAGATTTGGTGCCAAGGATCTATGAAATGATGGGTACGTA AAAACCCATCAAGTTT
GAAGATGTTTATGTCTGGGATCTGTTTGAATTTATTA AAAGTGAACATTCATATTCAGAAGA
CACAAATCTTTTCTTTCTATATAGAATCCATTTGGATGTCTGTCAACTGAGACGTGTGATTG
CAGCCCATGGCTTTTCTTCCAAGGAGATCATCACTTTTTTGGCAGGTCATGCTAAGGAACACC
ACATGCCATTATTAACTTCACATTCTACAAAAGCCTAGAAGGACAGGATACCTTGTGGAAA
GTGTTAAATAAAGTAGTACTGTGGAAAATTTCATGGGGAGGTCAGTGTGCTGGCTTACACTG
AACTGAAACTCATGAAAAACCCAGACTGGAGACTGGAGGGTTACACTTGTGATTTATTAGTC
AGGCCCTTCAAAGATGATATGTGGAGGAATTAAATATAAAGGAATTGGAGGTTTTTGCTAAA
GAAATTAATAGGACCAACAATTTGGACATGTCATTCTGTAGACTAGAATTTCTTAAAAGGG
TGTTACTGAGTTATAAGCTCACTAGGCTGTAAAAACAAAACAATGTAGAGTTTTATTATTG
AACAAATGTAGTCACTTGAAGGTTTTGTGTATATCTTATGTGGATTACCAATTTAAAAATATA
TGTTAGTTCTGTGTCAAAAACTTCTTCACTGAAGTTATACTGAACAAAATTTTACCTGTTTT
TGGTCATTTATAAAGTACTTCAAGATGTTGCAGTATTTACAGTTATTATTATTATAAATTA
CTTCAACTTTGTGTTTTTAAATGTTTTGACGATTTCAATACAAGATAAAAAGGATAGTGAAT
CATTCTTTACATGCAAACATTTCCAGTTACTTAACTGATCAGTTTATTATTGATACATCAC
TCCATTAATGTAAAGTCATAGGTCATTATTGCATATCAGTAATCTCTTGGACTTTGTAAAT
ATTTTACTGTGGTAATATAGAGAAGAATTAAAGCAAGAAAATCTGAAAA

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FIGURE 137

MASALWTVLPSRMSLRSLKWSLLLLSLLSFFVMWYLSLPHYNVIERVNWMYFYEYEPiYRQD
FHFTLREHSNCSHQNPFLVILVTSHPSDVKARQAIRVTWGEKKSWWGYEVLTFLLGQEA EK
EDKMLALSLEDEHLLYGDII RQDFLDTYNNLT LKTIMAFRWVTEFCPNAKYVMKTD TDVFIN
TGNLVKYLLNLNHSEKFFTGYPLIDNYSYRGFYQKTHISYQEYPFKVFPYCSGLGYIMSRD
LVPRIYEMMGHV KPIKFEDVYVGICLNLLKVNIHIPEDTNLFFLYRIHLDVCQLRRVIAAHG
FSSKEIITFWQVMLRNTTCHY

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FIGURE 138

CCTCTGTCCACTGCTTTTCGTGAAGACAAGATGAAGTTCACAATTGTCTTTGCTGGACTTCTT
GGAGTCTTTCTAGCTCCTGCCCTAGCTAACTATAATATCAACGTCAATGATGACAACAACAA
TGCTGGAAGTGGGCAGCAGTCAGTGAGTGTCAACAATGAACACAATGTGGCCAATGTTGACA
ATAACAACGGATGGGACTCCTGGAATTCATCTGGGATTATGGAAATGGCTTTGCTGCAACC
AGACTCTTTCAAAAAGAAGACATGCATTGTGCACAAAATGAACAAGGAAGTCATGCCCTCCAT
TCAATCCCTTGATGCACTGGTCAAGGAAAAGAAGCTTCAGGGTAAGGGACCAGGAGGACCAC
CTCCCAAGGGCCTGATGTACTCAGTCAACCCAAACAAAGTCGATGACCTGAGCAAGTTCGGA
AAAAACATTGCAAACATGTGTCGTGGGATTCCAACATACATGGCTGAGGAGATGCAAGAGGC
AAGCCTGTTTTTTTTACTCAGGAACGTGCTACACGACCAGTGTACTATGGATTGTGGACATTT
CCTTCTGTGGAGACACGGTGGAGAACTTAAACAATTTTTTAAAGCCACTATGGATTTAGTCAT
CTGAATATGCTGTGCAGAAAAAATATGGGCTCCAGTGGTTTTTACCATGTCATTCTGAAATT
TTTCTCTACTAGTTATGTTTGATTTCTTTAAGTTTCAATAAAATCATTTAGCATTGAAAAAA

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FIGURE 139

MKFTIVFAGLLGVFLAPALANYNINVNDDNNNAGSGQQSVSVNNEHNVANVDNNNGWDSWNS
IWDYGNGFAATRLFQKKTCIVHKMNKEVMPSIQSLDALVKEKKLQGKGPGGPPPKGLMYSVN
PNKVDDLKFGKNIANMCRGIPTYMAEEMQEASLFFYSGTCYTTSVLWIVDISFCGDTVEN

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FIGURE 140

CATTTCTGAACTAATCGTGTGAGAATTGACTTTGAAAAGCATTGCTTTTTACAGAAGTATA
TTAACTTTTTAGGAGTAATTTCTAGTTTGGATTGTAATATGAAATAATTTAAAAGGGCTTCG
CTCATATATAGGAAAAATCGCATATGGTCCTAGTATTAAATTCTTATTGCTTACTGATTTTTT
TGAGTTAAGAGTTGTTATATGCTAGAATATGAGGATGTGAATATAAATAAGAGAAGAAAAAA
GAATAAAGTAGATTGAGTCTCCAATTTTATGTAAGCTTCAGAAGAAGCTGGTTTGTGTACATG
CAAGCTTATAGTTGAAATATTTTTTCAGGAATTACATGAATGACAGTCTTCGAACCAATGTGT
TTGTTTCGATTTCAACCAGAGACTATAGCATGTGCTTGCATCTACCTTGCAGCTAGAGCACTT
CAGATTCCGTTGCCAACTCGTCCCCATTGGTTTCTTCTTTTGGTACTACAGAAGAGGAAAT
CCAGGAAATCTGCATAGAAACACTTAGGCTTTATACCAGAAAAAGCCAACTATGAATTAC
TGAAAAAGAAGTAGAAAAAGAAAAGTAGCCTTACAAGAAGCCAAATTTAAAAGCAAAGGGA
TTGAATCCGGATGGAAGCTCCAGCCCTTTCAACCTGGGTGGATTTTCTCCAGCCTCCAAGCC
ATCATCACCAGAGAAGTAAAAGCTGAAGAGAAATCACCAATCTCCATTAATGTGAAGACAG
TCAAAAAAGAACCTGAGGATAGACAACAGGCTTCCAAAAGCCCTTACAATGGTGTAAGAAAA
GACAGCAAGAGAAGTAGAAATAGCAGAAGTGCAAGTCGATCGAGGTCAAGAACACGATCACG
TTCTAGATCACATACTCCAAGAAGACACTATAATAATAGGCGGAGTCGATCTGGAACATACA
GCTCGAGATCAAGAAGCAGGTCCCGCAGTCACAGTGAAAGCCCTCGAAGACATCATAATCAT
GGTTCTCCTCACCTTAAGGCCAAGCATACCAGAGATGATTTAAAAAGTTCAAACAGACATGG
TCATAAAAGGAAAAAATCTCGTTCTCGATCTCAGAGCAAGTCTCGGGATCACTCAGATGCAG
CCAAGAAACACAGGCATGAAAGGGGACATCATAGGGACAGGCGTGAACGATCTCGCTCCTTT
GAGAGGTCCATAAAAGCAAGCACCATGGTGGCAGTCGCTCAGGACATGGCAGGCACAGGCG
CTGACTTTCTCTTCCTTTGAGCCTGCATCAGTTCTTGGTTTTGCCTATCTACAGTGTGATGT
ATGGACTCAATCAAAAACATTAAACGCAAAGTATTAGGATTTGATTTCTTGAAACCCTCTA
GGTCTCTAGAACACTGAGGACAGTTTCTTTTGAAAAGAACTATGTTAATTTTTTTGCACATT
AAAATGCCCTAGCAGTATCTAATTTAAAACCATGGTCAGGTTCAATTGTACTTTATTATAGT
TGTGTATTGTTTATTGCTATAAGAACTGGAGCGTGAATTCTGTAAAAATGTATCTTATTTTT
ATACAGATAAAATTGCAGACACTGTTCTATTTAAGTGGTTATTTGTTTAAATGATGGTGAAT
ACTTTCTTAACACTGGTTTGTCTGCATGTGTAAAGATTTTTTACAAGGAAATAAAATACAAAT
CTTGTTTTTTCTAAAAAAGAAAAAAGT

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FIGURE 141

MNDSLRTNVFVRFQPETIACACIYLAARALQIPLPTRPHWFLFLFGTTEEEIQEICIETLRLY
TRKKPNYELLEKEVEKRVKVALQEAKLKAKGLNPDGTPALSTLGGFSPASKPSSPREVKAEK
SPISINVKTVKKEPEDRQQASKSPYNGVRKDSKRSRNSRSASRSRSRTRSRSRSHTPRRHYN
NRRSRSGTYSSRSRSHSESPRRHHNHGSPHLKAKHTRDDLKSSNRHGHKRKKSRSRSQ
SKSRDHSDAAKKHRHERGHHRDRRERSRSFERSHKSKHHGGSRSRSGHGRHR

FIGURE 142

TGGGGATAAAGGAAAAATGGTCAGGTATTAATGGCTTAAAGATTATTGGAAGGGGTTTATCA
TTTTTTGAANNNTATTCGGGTCANAATTGNCTTTGAAAAGCATTGCTTTTTACAGAAATATAT
TANCTTTTTAGAGTAATTTCTAGTTTGGATTGTAATATGAAATTATTTAAAAGGGCTTCGCT
CATATATAGGAAAATCGCATATGGTCCTAGTATTAAATTNNTATTGCTTACTGATTTTTTTG
AGTTAAGAGTTGTTATATGNTAGAATATGAGGATGTGAATATAAATAAGAGAAGAAAAAGA
ATAAAGTAGATTGAGTCTCCAATTTTATGTAAGCTTCAGAAGAAGCTGGTTTGTTTACATGCA
AGCTTATAGTTGAAATATTTTTTCAGGAATTACATGAATGACAGTCTTCGAACCAATGTGTTT
GTTTCGATTTCAACCAGAGANTATAGCATGTGCTTGCATCTACCTTGCAGNTAGAGCACTTCA
GATTCCGTTGCCAACTNGTCCCCATTGGTTTCTTCTTTTTGGTACTACAGAAGAGGAAATCC
AGGAAATNTGCATAGAAACACTTAGGCTTTATACCAGAAAAAAGCCAACTATGAATTACTG
GAAAAAGAAGTAGAAAAAAGAAAAGTAGCCTTACAAGAAGCCNAATTAAAAGCAAAGGGATT
GAATCCGGATGGAACTCCAGCCCTTTCAACCCTGGGTGGATTTTCTCC

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FIGURE 143

GGCACGAGGCCTCGTGCCAAGCTTGGCACGAGGGTGACCGCGTTCTCGCACGCGTCAATGGC
GGTCCTCGGAGTACAGCTGGTGGTGACCCTGCTCACTGCCACCCTCATGCACAGGCTGGCGC
CACACTGCTCCTTCGCGCGCTGGCTGCTCTGTAACGGCAGTTTGTTCCGATACAAGCACCCG
TCTGAGGAGGAGCTTCGGGCCCTGGCGGGGAAGCCGAGGCCAGAGGCAGGAAAGAGCGGTG
GGCCAATGGCCTTAGTGAGGAGAAGCCACTGTCTGTGCCCCGAGATGCCCCGTTCCAGCTGG
AGACCTGCCCCCTCACGACCGTGGAATGCCCTGGTCCTGCGCTTCTTCCTGGAGTACCAGTGG
TTTGTGGACTTTGCTGTGTACTCGGGCGGCGTGTACCTCTTCACAGAGGCCTACTACTACAT
GCTGGGACCAGCCAAGGAGACTAACATTGCTGTGTTCTGGTGCCTGCTCACGGTGACCTTCT
CCATCAAGATGTTTCTGACAGTGACACGGCTGTACTTCAGCGCCGAGGAGGGGGGTGAGCGC
TCTGTCTGCCTCACCTTTGCCTTCCTCTTCCTGCTGCTGGCCATGCTGGTGCAAGTGGTGCG
GGAGGAGACCCTCGAGCTGGGCCTGGAGCCTGGTCTGGCCAGCATGACCCAGAACTTAGAGC
CACTTCTGAAGAAGCAGGGCTGGGACTGGGCGCTTCCTGTGGCCAAGCTGGCTATCCGCGTG
GGACTGGCAGTGGTGGGCTCTGTGCTGGGTGCCTTCCTCACCTTCCAGGCCTGCGGCTGGC
CCAGACCCACCGGGACGCACTGACCATGTCGGAGGACAGACCCATGCTGCAGTTCCTCTCTGC
ACACCAGCTTCCTGTCTCCCCTGTTTCATCCTGTGGCTCTGGACAAAGCCCATTGCACGGGAC
TTCCTGCACCAGCCGCCGTTTGGGGAGACGCGTTTCTCCCTGCTGTCCGATTCTGCCTTCGA
CTCTGGGCGCCTCTGGTTGCTGGTGGTGTGTGCCTGCTGCGGCTGGCGGTGACCCGGCCCC
ACCTGCAGGCCTACCTGTGCCTGGCCAAGGCCCGGGTGGAGCAGCTGCGAAGGGAGGCTGGC
CGCATCGAAGCCCGTGAAATCCAGCAGAGGGTGGTCCGAGTCTACTGCTATGTGACCGTGGT
GAGCTTGCAGTACCTGACGCCGCTCATCCTCACCTCAACTGCACACTTCTGCTCAAGACGC
TGGGAGGCTATTCTGGGGCCTGGGCCCAGCTCCTCTACTATCCCCGACCCATCCTCAGCC
AGCGCTGCCCCCATCGGCTCTGGGGAGGACGAAGTCCAGCAGACTGCAGCGCGGATTGCCGG
GGCCCTGGGTGGCCTGCTTACTCCCCTCTTCCTCCGTGGCGTCCTGGCCTACCTCATCTGGT
GGACGGCTGCCTGCCAGCTGCTCGCCAGCCTTTTCGGCCTCTACTTCCACCAGCACTTGGCA
GGCTCCTAGCTGCCTGCAGACCCTCCTGGGGCCCTGAGGTCTGTTCTGGGGCAGCGGGACA
CTAGCCTGCCCCCTCTGTTTGCGCCCCCGTGTCCCCAGCTGCAAGGTGGGGCCGGACTCCCC
GGCGTTCCCTTCACCACAGTGCCTGACCCGCGGCCCCCCTTGGACGCCGAGTTTCTGCCTCA
GAACTGTCTCTCCTGGGCCCAGCAGCATGAGGGTCCCAGGCCATTGTCTCCGAAGCGTATG
TGCCAGGTTTGAGTGGCGAGGGTGATGCTGGCTGCTCTTCTGAACAAATAAAGGAGCATGCC
GATTTTTTAA

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FIGURE 144

MAVLGVQLVVTLTATLMHRLAPHCSFARWLLCNGSLFRYKHPSEEEELRALAGKPRPRGRKE
RWANGLSEEKPLSVPRDAPFQLETCTTVDALVLRFFLEYQWFVDFAVYSGGVYLFTEAYY
YMLGPAKETNIAVFWCLLTVTFSIKMFLTVTRLYFSAEEGGERSVCLTFAFLFLLLAMLVQV
VREETLELGLPGLASMTQNLEPLLKKQGWDWALPVAKLAIRVGLAVVGSVLGAFLTFPGLR
LAQTHRDALTMSEDRPMLQFLLHTSFLSPLFILWLWTKPIARDFLHQPPFGETRFSLLSDSA
FDSGRLWLLVVLCLLRLAVTRPHLQAYLCLAKARVEQLRREAGRIEAREIQQRVVRVYCYVT
VVSILQYLTPILTLNCTLLKTLGGYSWGLGPAPLLSPDPSSASAAPIGSGEDEVQQTAAARI
AGALGGLLTPLFLRGVLAYLIWWTAAACQLLASLFGLYFHQHLAAGS

FIGURE 145

CGTTNGCACGCGTCAATGGCGGTCCCTCGGAGTACAGCTGGTGGTGACCCTGCTCACTGCCAC
CCTCATGCACAGGCTGGCGCCACACTGCTCCTTCGCGCGCTGGCTGCTCTGTAACGGCAGTT
TGTTCCGATACAAGCACCCGTNTTGAGGAGGAGCTTCGGGCCCTGGCGGGGAAGCCGAGGCC
CAGAGGCAGGAAAGAGCGGTGGGCCAATGGCCTTAGTGAGGAGAAGCCACTGTCTGTGCCCC
GAGATGCCCCGTTCCAGCTGGAGACCTGCCCCCTCACGACCGTGGATGCCCTGGTCCTGCGC
TTCTTCCTGGAGTACCAGTGGTTTGTGGACTTTGCTGTGTACTCGGGCGGCGTGTACCTCTT
CACAGAGGCCTACTACTACATGCTGGGACCAGCCAAGGAGACTAACATTGCTGTGTTCTGGT
GCCTGCTCACAGTGACCTTCTCCATCAAGATGTTCTGACAGTGACACGGCTGTACTTCAGC
GCCGAGGAGGGGGGTGAGCGCTCTGTCTGCCTCACCTTTGCCTTCCTCTTCCTGCTGCTGGC
CATGCTGGTGCAAGCG

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FIGURE 146

GGTTCCTACATCCTCTCATCTGAGAATCAGAGAGCATAATCTTCTTACGGGCCCCGTGATTTA
TTAACGTGGCTTAATCTGAAGGTTCTCAGTCAAATTCTTTGTGATCTACTGATTGTGGGGGC
ATGGCAAGGTTTGCTTAAAGGAGCTTGGCTGGTTTGGGCCCTTGCTAGCTGACAGAAGGTGGC
CAGGGAGAATGCAGCACACTGCTCGGAGAAATGAAGGCGCTTCTGTTGCTGGTCTTGCCTTGG
CTCAGTCCTGCTAACTACATTGACAATGTGGGCAACCTGCACTTCTGTATTGAGAACTCTG
TAAAGGTGCCTCCCACTACGGCCTGACCAAAGATAGGAAGAGGCGCTCACAAGATGGCTGTC
CAGACGGCTGTGCGAGCCTCACAGCCACGGCTCCCTCCCCAGAGGTTTCTGCAGCTGCCACC
ATCTCCTTAATGACAGACGAGCCTGGCCTAGACAACCCTGCCTACGTGTCCTCGGCAGAGGA
CGGGCAGCCAGCAATCAGCCCAGTGGACTCTGGCCGGAGCAACCGAACTAGGGCACGGCCCT
TTGAGAGATCCACTATTAGAAGCAGATCATTTAAAAAATAAATCGAGCTTTGAGTGTTCTT
CGAAGGACAAAGAGCGGGAGTGCAAGTGGCCAAACCATGCCGACCAGGGCAGGGAAAATTCTGA
AAACACCACTGCCCCCTGAAGTCTTTCCAAGGTTGTACCACCTGATTCCAGATGGTGAAATTA
CCAGCATCAAGATCAATCGAGTAGATCCCAGTGAAAGCCTCTCTATTAGGCTGGTGGGAGGT
AGCGAAACCCCACTGGTCCATATCATTATCCAACACATTTATCGTGATGGGGTGATCGCCAG
AGACGGCCGGCTACTGCCAGGAGACATCATTCTAAAGGTCAACGGGATGGACATCAGCAATG
TCCCTCACAACACTACGCTGTGCGTCTCCTGCGGCAGCCCTGCCAGGTGCTGTGGCTGACTGTG
ATGCGTGAACAGAAGTTCGCGAGCAGGAACAATGGACAGGCCCCGGATGCCTACAGACCCCG
AGATGACAGCTTTCATGTGATTCTCAACAAAAGTAGCCCCGAGGAGCAGCTTGGAATAAAAC
TGGTGCGCAAGGTGGATGAGCCTGGGGTTTTTCATCTTCAATGTGCTGGATGGCGGTGTGGCA
TATCGACATGGTCAGCTTGAGGAGAATGACCGTGTTAGCCATCAATGGACATGATCTTCG
ATATGGCAGCCCAGAAAGTGCGGCTCATCTGATTCAGGCCAGTGAAAGACGTGTTACCTCG
TCGTGTCCCGCCAGGTTCCGGCAGCGGAGCCCTGACATCTTTCAGGAAGCCGGCTGGAACAGC
AATGGCAGCTGGTCCCCAGGGCCAGGGGAGAGGAGCAACACTCCCAAGCCCCCTCCATCCTAC
AATTACTTGTATGAGAAGGTGGTAAATATCCAAAAGACCCCCGGTGAATCTCTCGGCATGA
CCGTGCGAGGGGGAGCATCACATAGAGAATGGGATTTGCCTATCTATGTCATCAGTGTTGAG
CCCGGAGGAGTCATAAGCAGAGATGGAAGAATAAAAACAGGTGACATTTTGTGTAATGTGGA
TGGGGTCGAACTGACAGAGGTCAGCCGGAGTGAGGCAGTGGCATTATTGAAAAGAACATCAT
CCTCGATAGTACTCAAAGCTTTGGAAGTCAAAGAGTATGAGCCCCAGGAAGACTGCAGCAGC
CCAGCAGCCCTGGACTCCAACCACAACATGGCCCCACCCAGTGACTGGTCCCCATCCTGGGT
CATGTGGCTGGAATTACCACGGTGCTTGTATAACTGTAAAGATATTGTATTACGAAGAAACA
CAGCTGGAAGTCTGGGCTTCTGCATTGTAGGAGGTTATGAAGAATACAATGGAAACAAACCT
TTTTTCATCAAATCCATTGTTGAAGGAACACCAGCATAACAATGATGGAAGAATTAGATGTGG
TGATATTCTTCTTGCTGTCAATGGTAGAAGTACATCAGGAATGATACATGCTTGCTTGGCAA
GACTGCTGAAAGAACTTAAAGGAAGAATTACTCTAACTATTGTTTCTTGGCCTGGCACTTTT
TTATAGAATCAATGATGGGTGAGAGGAAAACAGAAAAATCACAAATAGGCTAAGAAGTTGAA
ACACTATATTTATCTTGTGTCAGTTTTTATATTTAAAGAAAGAATACATTGTAAAAATGTCAGG
AAAAGTATGATCATCTAATGAAAGCCAGTTACACCTCAGAAAAATATGATTCCAAAAAAATTA
AACTACTAGTTTTTTTTTTCAGTGTGGAGGATTTCTCATTACTCTACAACATTGTTTATATTT
TTTCTATTCAATAAAAAGCCCTAAAACACTAAAATGATTGATTGTATACCCCACTGAATT
CAAGCTGATTTAAATTTAAATTTGGTATATGCTGAAGTCTGCCAAGGGTACATTATGGCCA
TTTTTAATTTACAGCTAAAATATTTTTTAAATGCATTGCTGAGAAACGTGCTTTTCATCAA
ACAAGAATAAATATTTTTTCAGAAGTTAAA

FIGURE 147

MKALLLLVLPWLSPANYIDNVGNLHFLYSELCKGASHYGLTKDRKRRSQDGCPCDGCASLTAT
APSPEVSAAATISLMTDEPGLDNPAYVSSAEDGQPAISPVDSGRSNRTRARPFERSTIRSRS
FKKINRALSVLRRTKSGSAVANHADQGRENSENTTAPEVFPRLYHLIPDGEITSIKINRVDP
SESLSIRLVGGSETPLVHII IQHIYRDGVIARDGRLLPGDIILKVNGMDISNVPHNYAVRLL
RQPCQVLWLTVMREQKFRSRNNGQAPDAYRPRDDSFHVILNKSSPEEQLGIKLVKRVDEPGV
FIFNVLDGGVAYRHGQLEENDRVLAINGHDLRYGSPESAHLIQASERRVHLVVSQRQVRQRS
PDIFQEAGWNSNGSWSPGPGERSNTPKPLHPTITCHEKVVNIQKDPGESLGMTVAGGASHRE
WDLPIYVISVEPGGVISRDGRIKTGDILLNVDGVELTEVSRSEAVALLKRTSSSIVLKALEV
KEYEPQEDCSSPAALDSNHNMAPPSDWSPSWMWLELPRCLYNCKDIVLRRNTAGSLGFCIV
GGYEEYNGNKPFPIKSIVEGTPAYNDGRIRCGDILLAVNGRSTSGMIHACLARLLKELKGRI
TLTIVSWPGTFL

FIGURE 148

CCAAAGTGATCATTTGAAAAAGAGATATCCACATCTTCAAGCCCATATAAAGGATAGAAGCT
GCACAGGGCAGCTTTACTTACTCCAGCACCTTCCTCTCCCAGGCAAATGGTGCTGACCATCT
TTGGGATACAATCTCATGGATACGAGGTTTTTAACATCATCAGCCCAAGCAACAATGGTGGC
AATGTTTCAGGAGACAGTGACAATTGATAATGAAAAAATACCGCCATCGTTAACATCCATGC
AGGATCATGCTCTTCTACCACAATTTTGAATAAATCATGGCTACATTGCATCCAGGGTGC
TCTCCCGAAGAGCCTGCTTTATCCTGAAGATGGACCATCAGAACATCCCTCCTCTGAACAAT
CTCCAATGGTACATCTATGAGAAACAGGCTCTGGACAACATGTTCTCCAACAAATACACCTG
GGTCAAGTACAACCCTCTGGAGTCTCTGATCAAAGACGTGGATTGGTTCTGCTTGGGTCAC
CCATTGAGAACTCTGCAAACATATCCCTTTGTATAAGGGGGAAGTGGTTGAAAACACACAT
AATGTCGGTGCTGGAGGCTGTGCAAAGGCTGGGCTCCTGGGCATCTTGGGAATTTCAATCTG
TGCAGACATTCATGTTTAGGATGATTAGCCCTCTTGTTTTATCTTTTCAAAGAAATACATCC
TTGGTTTACACTCAAAGTCAAATTAAATTCTTTCCCAATGCCCCAACTAATTTTGAGATTC
AGTCAGAAAATATAAATGCTGTATTTATA

FIGURE 149

MKILVAFLVLTIFGIQSHGYEVFNIISPSNNGGNVQETVTIDNEKNTAIVNIHAGSCSSTT
IFDYKHGYIASRVLSRRACFILKMDHQNIPLNNLQWYIYEKQALDNMFSNKYTWVKYNPLE
SLIKDVDWFLLGSPIEKLCKHIPLYKGEVVENTHNVGAGGCAKAGLLGILGISICADIHV

FIGURE 150

GGCACGAGCCAGGAAC TAGGAGGTTCTCACTGCCCCGAGCAGAGGCCCTACACCCACCGAGGC
ATGGGGCTCCCTGGGCTGTTCTGCTTGGCCGTGCTGGCTGCCAGCAGCTTCTCCAAGGCACG
GGAGGAAGAAATTACCCCTGTGGTCTCCATTGCCTACAAAGTCCTGGAAGTTTCCCCAAAG
GCCGCTGGGTGCTCATAACCTGCTGTGCACCCAGCCACCACCGCCCATCACCTATTCCCTC
TGTGGAACCAAGAACATCAAGGTGGCCAAGAAGGTGGTGAAGACCCACGAGCCGGCCTCCTT
CAACCTCAACGTCACACTCAAGTCCAGTCCAGACCTGCTCACCTACTTCTGCCGGGCGTCCT
CCACCTCAGGTGCCCATGTGGACAGTGCCAGGCTACAGATGCACTGGGAGCTGTGGTCCAAG
CCAGTGTCTGAGCTGCGGGCCAACCTTCACTCTGCAGGACAGAGGGGCAGGCCCCAGGGTGGA
GATGATCTGCCAGGCGTCCTCGGGCAGCCACCTATCACCAACAGCCTGATCGGGAAGGATG
GGCAGGTCCACCTGCAGCAGAGACCATGCCACAGGCAGCCTGCCAACTTCTCCTTCTGCCG
AGCCAGACATCGGACTGGTTCTGGTGCCAGGCTGCAAAACAACGCCAATGTCCAGCACAGCGC
CCTCACAGTGGTGCCCCCAGGTGGTGACCAGAAGATGGAGGACTGGCAGGGTCCCCTGGAGA
GCCCCATCCTTGCCCTTGCCGCTCTACAGGAGCACCCGCCGTCTGAGTGAAGAGGAGTTTGGG
GGGTTCAGGATAGGGAATGGGGAGGTGAGAGGACGCAAAGCAGCAGCCATGTAGAATGAACC
GTCCAGAGAGCCAAGCACGGCAGAGGACTGCAGGCCATCAGCGTGCACTGTTTCGTATTTGGA
GTTTCATGCAAAATGAGTGTGTTTTAGCTGCTCTTGCCACAAAAAAAAAAAAAAAAAAAAA

FIGURE 151

MGLPGLFCLAVLAASSFSKAREEEITPVVSIAYKVLEVFPKGRWVLITCCAPQPPPPITYSL
CGTKNIKVAKKVVKTHEPASFNLNVTLKSSPDLLTYFCRASSTSGAHVDSARLQMHWELWSK
PVSELNANFTLQDRGAGPRVEMICQASSGSPPITNSLIGKDGQVHLQQRPCHRQPANFSFLP
SQTSDWFWCQAANNANVQHSALTVPVPGGDQKMEDWQGPLESPILALPLYRSTRRLSEEEFG
GFRIGNGEVRGRKAAAM

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FIGURE 152

GGTCCTTAATGGCAGCAGCCGCCGCTACCAAGATCCTTCTGTGCCTCCCGCTTCTGCTCCTG
CTGTCCGGCTGGTCCCGGGCTGGGCGAGCCGACCCTCACTCTCTTTGCTATGACATCACCGT
CATCCCTAAGTTCAGACCTGGACCACGGTGGTGTGCGGTTCAAGGCCAGGTGGATGAAAAGA
CTTTTCTTCACTATGACTGTGGCAACAAGACAGTCACACCTGTCAGTCCCCTGGGGAAGAAA
CTAAATGTCAACAACGGCCTGGAAAGCACAGAACCCAGTACTGAGAGAGGTGGTGGACATACT
TACAGAGCAACTGCGTGACATTCACTGGAGAATTACACACCCAAGGAACCCCTCACCTGC
AGGCAAGGATGTCTTGTGAGCAGAAAGCTGAAGGACACAGCAGTGGATCTTGGCAGTTCAGT
TTCGATGGGCAGATCTTCCTCCTCTTTGACTCAGAGAAGAGAATGTGGACAACGGTTCATCC
TGGAGCCAGAAAGATGAAAGAAAAGTGGGAGAATGACAAGGTTGTGGCCATGTCCTTCCATT
ACTTCTCAATGGGAGACTGTATAGGATGGCTTGAGGACTTCTTGATGGGCATGGACAGCACC
CTGGAGCCAAGTGCAGGAGCACCCTCGCCATGTCTCAGGCACAACCCAACCTCAGGGCCAC
AGCCACCACCCTCATCCTTTGCTGCCTCCTCATCATCCTCCCCTGCTTCATCCTCCCTGGCA
TCTGAGGAGAGTCCTTTAGAGTGACAGGTAAAGCTGATACCAAAGGCTCCTGTGAGCAGG
GTCTTGATCAAACCTCGCCCTTCTGTCTGGCCAGCTGCCACGACCTACGGTGTATGTCCAGT
GGCCTCCAGCAGATCATGATGACATCATGGACCCAATAGCTCATTCACTGCCTTGATTCTT
TTGCCAACAAATTTTACCAGCAGTTATACCTAACATATTATGCAATTTTCTCTTGGTGCTACC
TGATGGAATTCCTGCACTTAAAGTTCTGGCTGACTAAACAAGATATATCATTTTCTTTCTTC
TCTTTTTGTTTGAAAATCAAGTACTTCTTTGAATGATGATCTCTTTCTTGCAAATGATATT
GTCAGTAAAATAATCACGTTAGACTTCAGACCTCTGGGGATTCTTCCGTGTCTGAAAGAG
AATTTTTAAATTATTTAATAAGAAAAAATTTATATTAATGATTGTTTCCTTTAGTAATTTAT
TGTTCTGTACTGATATTTAAATAAGAGTTCTATTTCCCAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 153

MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRWCAVQGQVDEKTFL
HYDCGNKTVTPVSPLGKKLNVTAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLTLQAR
MSCEQKAEGHSSGSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAMSFHYFS
MGDCIGWLEDFLMGMDSTLEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPCFILPGI

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FIGURE 154

GGGAAAGCCATTTGAAAACCCATCTATACAACTATATATTTTCATTTCTGCTGCTAGCTG
CCTTGGGCCTCACAATTTTCATTCTGTTTTCTGACTTTCAAGTTATATACCGTGGAATGGAG
TTGATCCCAACCATAACATCGTGGAGGGTTTTAATTTTGGTGGTAGCCCTCACCCAATTCTG
GTGTGGCTTTCTTTGCAGAGGATTCCACCTTCAAAATCATGAACTCTGGCTGTTGATCAAAA
GAGAATTTGGATTCTACTCTAAAAGTCAATATAGGACTTGGCAAAAGAAGCTAGCAGAAGAC
TCAACCTGGCCTCCCATAAACAGGACAGATTATTCAGGTGATGGCAAAAATGGATTCTACAT
CAACGGAGGCTATGAAAGCCATGAACAGATTCCAAAAAGAAAACCTCAAATTGGGAGGCCAAC
CCACAGAACAGCATTCTGCGCCAGGCTGTAATCAGAATTGTCGTCGTACATGCTCAACAGC
ATTGCTTTTTTCCCCAAAATTAACACATTGTGGAGAAGTGATGATACTCTCCCCTTACCTTT
CCTCTCTCCATTCAAGCATTCAAAGTATATTTTCAATGAATTAAACCTTGCAGCAAGGGACC
TTAGATAGGCTTATTCTGACTGTATGCTTTACCAATGAGAGAAAAAAATGCATTTCTGTAT
CATCCTTTTCAATAAACTGTATTTCATTTTGAAAAAAAAAAAAAAAAAAAAA

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FIGURE 155

MELIPTITSWRVLILVVALTQFWCGFLCRGFHLQNHFWLLIKREFGFYSKSQYRTWQKKLA
EDSTWPPINRTDYSGDGKNGFYINGGYESHEQIPKRKLKLGQPTQHFWARL

FIGURE 156

GTTCTCCTTTCCGAGCCAAAATCCCAGGCGATGGTGAATTATGAACGTGCCACACCATGAAG
CTCTTGTTGGCAGGTAACCTGTGCACCACCACACCTGGAATGCCATCCTGCTCCCGTTTCGTCTA
CCTCACGGCGCAAGTGTGGATTCTGTGTGCAGCCATCGCTGCTGCCGCCTCAGCCGGGCCCC
AGAACTGCCCCCTCCGTTTGCTCGTGCAGTAACCAGTTCAGCAAGGTGGTGTGCACGCGCCGG
GGCCTCTCCGAGGTCCCGCAGGGTATTCCTCGAACACCCGGTACCTCAACCTCATGGAGAA
CAACATCCAGATGATCCAGGCCGACACCTTCCGCCACCTCCACCACCTGGAGGTCCTGCAGT
TGGGCAGGAACCTCCATCCGGCAGATTGAGGTGGGGGCCTTCAACGGCCTGGCCAGCCTCAAC
ACCCTGGAGCTGTTTCGACAACTGGCTGACAGTCATCCCTAGCGGGGCCTTTGAATACCTGTC
CAAGCTGCGGGAGCTCTGGCTTCGCAACAACCCCATCGAAAGCATCCCCTCTTACGCCTTCA
ACCGGGTGGCCTCCCTCATGCGCCTGGACTTGGGGGAGCTCAAGAAGCTGGAGTATATCTCT
GAGGGAGCTTTTGAGGGGCTGTTCAACCTCAAGTATCTGAACTTGGGCATGTGCAACATTAA
AGACATGCCCAATCTCACCCCCCTGGTGGGGCTGGAGGAGCTGGAGATGTCAGGGAACCACT
TCCCTGAGATCAGGCCTGGCTCCTTCCATGGCCTGAGCTCCCTCAAGAAGCTCTGGGTCTATG
AACTCACAGGTCAGCCTGATTGAGCGGAATGCTTTTGACGGGCTGGCTTCACTTGTGGAAC
CAACTTGGCCCAACAATAACCTCTCTTCTTTGCCCCATGACCTCTTTACCCCGCTGAGGTACC
TGGTGGAGTTGCATCTACACCACAACCCTTGGAACTGTGATTGTGACATTCTGTGGCTAGCC
TGGTGGCTTCGAGAGTATATACCCACCAATTCCACCTGCTGTGGCCGCTGTCATGCTCCCAT
GCACATGCGAGGCCGCTACCTCGTGGAGGTGGACCAGGCCTCCTTCCAGTGCTCTGCCCCCT
TCATCATGGACGCACCTCGAGACCTCAACATTTCTGAGGGTCGGATGGCAGAACTTAAGTGT
CGGACTCCCCCTATGTCTCCGTGAAGTGGTTGCTGCCCAATGGGACAGTGCTCAGCCACGC
CTCCCGCCACCCAAGGATCTCTGTCTCAACGACGGCACCTTGAACCTTTTCCACGTGCTGC
TTTCAGACACTGGGGTGTACACATGCATGGTGACCAATGTTGCAGGCAACTCCAACGCCTCG
GCCTACCTCAATGTGAGCACGGCTGAGCTTAACACCTCCAACCTACAGCTTCTTCACCACAGT
AACAGTGGAGACCACGGAGATCTCGCCTGAGGACACAACGCGAAAGTACAAGCCTGTTCCCTA
CCACGTCCACTGGTTACCAGCCGGCATATACCACCTCTACCACGGTGCTCATTGAGACTACC
CGTGTGCCCCAAGCAGGTGGCAGTACCCGCGACAGACACCACTGACAAGATGCAGACCAGCCT
GGATGAAGTCATGAAGACCACCAAGATCATCATTGGCTGCTTTGTGGCAGTGAAGTCTGCTAG
CTGCCGCCATGTTGATTGTCTTCTATAAACTTCGTAAGCGGCACCAGCAGCGGAGTACAGTC
ACAGCCGCCCGGACTGTTGAGATAATCCAGGTGGACGAAGACATCCCAGCAGCAACATCCGC
AGCAGCAACAGCAGCTCCGTCCGGTGTATCAGGTGAGGGGGCAGTAGTGCTGCCCAACAATTC
ATGACCATATTAATAACAACCTACAAACCAGCACATGGGGCCCACTGGACAGAAAACAGC
CTGGGGAACTCTCTGCACCCACAGTCACCACTATCTCTGAACCTTATATAATTGAGACCA
TACCAAGGACAAGGTACAGGAACTCAAAATATGAAGTCTCCCTCCCCCAAAAAAATTTATAAAAT
GCAATAGAATGCACACAAAGACAGCAACTTTTGTACAGAGTGGGGAGAGACTTTTCTTGTA
TATGCTTATATATTAAGTCTATGGGCTGGTTAAAAAACAAGATTATATTAATAATTAAAGA
CAAAAAGTCAAAACA

FIGURE 157

MKLLWQVTVHHHTWNAILLPFVYLTAQVWILCAAIAAAASAGPQNCPSVCSCSNQFSKVVCT
RRGLSEVPQGIPSNTRYLNLMMENNIQMIQADTFRHLHHLEVLQLGRNSIRQIEVGAFNGLAS
LNTLELFDNWLTVIPSGAFEYLSKLRELWLRNNPIESIPSYAFNRVPPLMRDLGELKKLEY
ISEGAFEGFLNLKYLNLGMCNIKDMPNLTPLVGLLEELEMSGNHFPFIRPGSFHGLSSLKKLW
VMNSQVSLIERNAFDGLASLVELNLAHNNLSSLPHDLFTPLRYLVELHLHNPWNCDCDILW
LAWWLREYIPTNSTCCGRCHAPMHMRGRYLVEVDQASFQCSAPFIMDAPRDLNISEGRMAEL
KCRTPPMSSVKWLLPNGTVLSHASRHPRISVLNDGTLNFSHVLLSDTGVYTCMVTVNAGNSN
ASAYLNVSTAE LN TSNYSFFT VTVETTEISPEDTTRKYKPVPTTSTGYQPAYTTSTTVLIQ
TTRVPKQVAVPATDTTDMQTSLEVMKTTKIIIGCFVAVTLLAAAMLIVFYKLRKRHQQRS
TVTAARTVEIIQVDEDIPAATSAAATAAPSGVSGEGAVVLPTIHDHINYNTYKPAHGAHWTE
NSLGNSLHPTVTTISEPYIIQTHTKDKVQETQI

FIGURE 158

[illegible]

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FIGURE 159

MELGCWTQLGLTFLQLLLISSLPREYTVINEACPGAENIMCRECCEYDQIECVCPGKREVV
GYTIPCCRNEENECDSCLIHPGCTIFENCKSCRNGSWGGLDDFYVKGIFYCAECRAGWYGGD
CMRCGQVLRAPKGQILLESYPLNAHCEWTIHAKPGFVIQLRFVMLSLEFDYMCQYDYVEVRD
GDNRDGQIIKRVCGNERPAPIQSIGSSLHVLHSDGSKNFDGFGHAIYEEITACSSSPCFHDG
TCVLDKAGSYKACLAGYTGQRCENLLEERNCSDFGGPVNGYQKITGGPGLINGRHAKIGTV
VSFFCNNSYVLSGNEKRTCQONGEWSGKQPICIKACREPKISDLVRRRVLPMQVQSRETPLH
QLYSAAFSKQKLQSAPTKKPALPFGDLPMGYQHLHTQLQYECISPFYRRLGSSRRTCLRTGK
WSGRAPSCIPICGKIENITAPKTQGLRWPWQAAIYRRTSGVHDGSLHKGAWFLVCSGALVNE
RTVVAAHCVTDLGKVTMIKTADLKVVVLGKFYRDDDRDEKTIQSLQISAILHPNYDPILLD
ADIAILKLLDKARISTRVQPICLAASRDLSTSFOESHITVAGWNVLADVRSPGFKNDTLRSG
VVSVDSELLCEEQHEDHGIPVSVTDNMFCASWEPTAPSDICTAETGGIAAVSFPGRASPEPR
WHLMGLVSWSYDKTCSHRLSTAFTKVLPFKDWIERNMK

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FIGURE 160

ACCAGGCATTGTATCTTCAGTTGTCATCAAGTTCGCAATCAGATTGGAAAAGCTCAACTTGA
AGCTTTCTTGCCTGCAGTGAAGCAGAGAGATAGATATTATTACGTAATAAAAAACATGGGC
TTCAACCTGACTTTCCACCTTTCCTACAAATTCCGATTACTGTTGCTGTTGACTTTGTGCCT
GACAGTGGTTGGGTGGGCCACCAGTAACTACTTCGTGGGTGCCATTCAAGAGATTCCCTAAAG
CAAAGGAGTTCATGGCTAATTTCCATAAGACCCTCATTTTGGGGAAGGGAAAACTCTGACT
AATGAAGCATCCACGAAGAAGGTAGAACTTGACAACTGTCCTTCTGTGTCTCCTTACCTCAG
AGGCCAGAGCAAGCTCATTTTCAAACAGATCTCACTTTGGAAGAGGTACAGGCAGAAAATC
CCAAAGTGTCCAGAGGCCGGTATCGCCCTCAGGAATGTAAAGCTTTACAGAGGGTCGCCATCCTC
GTTCCCCACCGGAACAGAGAGAAACACCTGATGTACCTGCTGGAACATCTGCATCCCTTCCT
GCAGAGGCAGCAGCTGGATTATGGCATCTACGTCACTCCACCAGGCTGAAGGTAAAAAGTTTA
ATCGAGCCAACTCTTGAATGTGGGCTATCTAGAAGCCCTCAAGGAAGAAAATTGGGACTGC
TTTATATTCCACGATGTGGACCTGGTACCCGAGAATGACTTTAACCTTTACAAGTGTGAGGA
GCATCCCAAGCATCTGGTGGTTGGCAGGAACAGCACTGGGTACAGGTTACGTTACAGTGGAT
ATTTTGGGGGTGTTACTGCCCTAAGCAGAGAGCAGTTTTCAAGGTGAATGGATTCTCTAAC
AACTACTGGGGATGGGGAGGCGAAGACGATGACCTCAGACTCAGGGTTGAGCTCCAAAGAAT
GAAAATTTCCCGGCCCTGCCTGAAGTGGGTAAATATACAATGGTCTTCCACACTAGAGACA
AAGGCAATGAGGTGAACGCAGAACGGATGAAGCTCTTACACCAAGTGTACGAGTCTGGAGA
ACAGATGGGTTGAGTAGTTGTTCTTATAAATTAGTATCTGTGGAACACAATCCTTTATATAT
CAACATCACAGTGGATTTCTGGTTTGGTGCATGACCCTGGATCTTTTGGTGATGTTTGGAG
AACTGATTCTTTGTTTGCAATAATTTTGGCCTAGAGACTTCAAATAGTAGCACACATTAAGA
ACCTGTTACAGCTCATTGTTGAGCTGAATTTTTCTTTTGTATTTTCTTAGCAGAGCTCCT
GGTGATGTAGAGTATAAAACAGTTGTAACAAGACAGCTTTCTTAGTCATTTTGATCATGAGG
GTTAAATATTGTAATATGGATACTTGAAGGACTTTATATAAAAGGATGACTCAAAGGATAAA
ATGAACGCTATTTGAGGACTCTGGTTGAAGGAGATTTATTTAAATTGAAGTAATATATTAT
GGGATAAAAGGCCACAGGAAATAAGACTGCTGAATGTCTGAGAGAACCAGAGTTGTTCTCGT
CCAAGGTAGAAAGGTACGAAGATACAATACTGTTATTCACTTATCCTGTACAATCATCTGTG
AAGTGGTGGTGTCAGGTGAGAAGGCGTCCACAAAAGAGGGGAGAAAAGGCGACGAATCAGGA
CACAGTGAACCTTGGGAATGAAGAGGTAGCAGGAGGGTGGAGTGTCTGCTGCAAAGGCAGCAG
TAGCTGAGCTGGTTGCAGGTGCTGATAGCCTTCAGGGGAGGACCTGCCAGGTATGCCTTCC
AGTGATGCCCCACCAGAGAATACATTCTCTATTAGTTTTTAAAGAGTTTTTGTAAAATGATTT
TGTACAAGTAGGATATGAATTAGCAGTTTACAAGTTTACATATTAATAATAATAATATGT
CTATCAAATACCTCTGTAGTAAAATGTGAAAAAGCAAAA

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FIGURE 161

MGFNLT FHLSYKFRL LLLTLCLTVVGWATS NYFVGAIQEIPKAKEFMANFHKTLILGKGKT
LTNEASTKKVELDNCPSPYLRGQSKLIFKPDLTLEEVQAENPKVSRGRYPQECKALQRV
AILVPHRNREKHLMYLLEHLHPFLQRQQLDYGIYVIHQAEKGKFNRAKLLNVGYLEALKEEN
WDCFIFHDVDLVPENDFNLYKCEEHPKHLVVGRNSTGYRLRYSGYFGGVTALSREQFFKVNG
FSNNYWGWGGEDDDLRLRVELQRMKISRPLPEVGKYTMVFHTRDKGNEVNAERMKLLHQVSR
VWRTDGLSSCSYKLVSVEHNPLYINITVDFWFGA

Important features:

Signal peptide:

amino acids 1-27

N-glycosylation sites:

amino acids 4-7, 220-223 and 335-338

Xylose isomerase proteins:

amino acids 191-201

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FIGURE 162

CGTGGGCCGGGGTTCGCGCAGCGGGCTGTGGGCGCGCCCGGAGGAGCGACCGCCGCAGTTCTC
GAGCTCCAGCTGCATTCCCTCCGCGTCCGCCCCACGCTTCTCCCGCTCCGGGCCCCGCAATG
GCCCAGGCAGTGTGGTCGCGCCTCGGCCGCATCCTCTGGCTGCCTGCCTCCTGCCCTGGGC
CCCGGCAGGGGTGGCCGCAGGCCTGTATGAACTCAATCTCACCACCGATAGCCCTGCCACCA
CGGGAGCGGTGGTGACCATCTCGGCCAGCCTGGTGGCCAAGGACAACGGCAGCCTGGCCCTG
CCCGCTGACGCCCACCTCTACCGCTTCCACTGGATCCACACCCCGCTGGTGTCTACTGGCAA
GATGGAGAAGGGTCTCAGCTCCACCATCCGTGTGGTGGGCCACGTGCCCCGGGAATTCCCGG
TCTCTGTCTGGGTCACTGCCGCTGACTGCTGGATGTGCCAGCCTGTGGCCAGGGGCTTTGTG
GTCCTCCCCATCACAGAGTTCCTCGTGGGGGACCTTGTTGTCACCAGAACAATTCCCTACC
CTGGCCCAGCTCCTATCTCACTAAGACCGTCTCTGAAAGTCTCCTTCCTCCTCCACGACCCGA
GCAACTTCCTCAAGACCGCCTTGTTTCTCTACAGCTGGGACTTCGGGGACGGGACCCAGATG
GTGACTGAAGACTCCGTGGTCTATTATAACTATTCCATCATCGGGACCTTCACCGTGAAGCT
CAAAGTGGTGGCGGAGTGGGAAGAGGTGGAGCCGGATGCCACGAGGGCTGTGAAGCAGAAGA
CCGGGGACTTCTCCGCCTCGCTGAAGCTGCAGGAAACCTTCGAGGCATCCAAGTGTGGGG
CCCACCCTAATTAGACCTTCCAAAAGATGACCGTGACCTTGAACCTTCCTGGGGAGCCCTCC
TCTGACTGTGTGCTGGCGTCTCAAGCCTGAGTGCCTCCCGCTGGAGGAAGGGGAGTGCCACC
CTGTGTCCGTGGCCAGCACAGCGTACAACCTGACCCACACCTTCAGGGACCTGGGGACTAC
TGCTTCAGCATCCGGGCCGAGAATATCATCAGCAAGACACATCAGTACCACAAGATCCAGGT
GTGGCCCTCCAGAATCCAGCCGGCTGTCTTTGCTTTCCCATGTGCTACACTTATCACTGTGA
TGTTGGCCTTCATCATGTACATGACCTGCGGAATGCCACTCAGCAAAAGGACATGGTGGAG
AACCCGGAGCCACCCTCTGGGGTCAAGTGTGCTGCCAGATGTGCTGTGGGCCTTTCTTGCT
GGAGACTCCATCTGAGTACCTGGAAATTGTTCTGTGAGAACCACGGGCTGCTCCCGCCCTCT
ATAAGTCTGTCAAACTTACACCGTGTGAGCACTCCCCCTCCCCACCCCATCTCAGTGTTAA
CTGACTGCTGACTTGGAGTTTCCAGCAGGGTGGTGTGCACCACTGACCAGGAGGGGTTTATT
TGCGTGGGGCTGTTGGCCTGGATCATCCATCCATCTGTACAGTTCAGCCACTGCCACAAGCC
CCTCCCTCTCTGTACCCCTGACCCAGCCATTACCCATCTGTACAGTCCAGCCACTGACA
TAAGCCCCACTCGGTTACCACCCCTTGACCCCTACCTTTGAAGAGGCTTCGTGCAGGACT
TTGATGCTTGGGGTGTTCGTGTTGACTCCTAGGTGGGCCTGGCTGCCCCACTGCCATTCT
CTCATATTGGCACATCTGCTGTCCATTGGGGGTCTCAGTTTCTCCCCAGACAGCCCTAC
CTGTGCCAGAGAGCTAGAAAGAAGGTATAAAGGGTTAAAAATCCATAACTAAAGGTTGTAC
ACATAGATGGGCACACTCACAGAGAGAAGTGTGCATGTACACACACCACACACACACACA
CACACACACACAGAAATATAAACACATGCGTCACATGGGCATTTAGATGATCAGCTCTGTA
TCTGGTTAAGTCGGTTGCTGGGATGCACCTGCACTAGAGCTGAAAGGAAATTTGACCTCCA
AGCAGCCCTGACAGGTTCTGGGCCCCGGGCCCTCCCTTTGTGCTTTGTCTCTGCAGTTCTTGC
GCCCTTTATAAGGCCATCCTAGTCCCTGCTGGCTGGCAGGGGCTGGATGGGGGGCAGGACT
AATACTGAGTGATTGCAGAGTGCTTTATAAATATCACCTTATTTTATCGAAACCCATCTGTG
AAACTTTTCACTGAGGAAAAGGCCTTGACGCGGTAGAAGAGGTTGAGTCAAGGCCGGGCGCGG
TGGCTCACGCCTGTAATCCAGCACTTTGGGAGGCCGAGGCGGGTGGATCACGAGATCAGGA
GATCGAGACCACCCTGGCTAACACGGTGAACCCCGTCTCTACTAAAAAATACAAAAGTT
AGCCGGGCGTGGTGGTGGTGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATG
GTGCGAACC CGGAGGCGGAGCTTGACGTGAGCCAGATGGCGCCACTGCACTCCAGCCTGA
GTGACAGAGCGAGACTCTGTCTCCA

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FIGURE 163

MAQAVWSRLGRILWLACLLPWAPAGVAAGLYELNLTTDSPATTGAVVTISASLVAKDNGSLA
LPADAHLYRFHWIHTPLVLTGKMEKGLSSTIRVVGHVPGEFPVSVWVTAADCWMCQPVARGF
VVLPITEFLVGDLVVTQNTSLPWPSSYLTKTVLKVSFLLHDP SNFLKTALFLYSWDFGDGTQ
MVTEDSVVYYNYSIIGTFTVKLKVVAEWEEVEPDATRAVKQKTGDFSASLKLQETLRGIQVL
GPTLIQTFQKMTVTNLNFGSPPLTVCWRLKPECLPLEEGECHPVSVASTAYNLTHTFRDPGD
YCFSIRAENIISKTHQYHKIQVWPSRIQPAVFAFPCATLITVMLAFIMYMTLRNATQQKDMV
ENPEPPSGVRCCCQMC CGPFLLET PSEYLEIVRENHGLLPPLYKSVKTYTV

Important features of the protein:

Signal peptide:

amino acids 1-24

Transmembrane domain:

amino acids 339-362

N-glycosylation sites.

amino acids 34-37, 58-61, 142-145, 197-200, 300-303 and 364-367

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FIGURE 165

MALSSQIWAACLLLLLLLLASLTSGSVFPQQTGQLAELQPQDRAGARASWMPMFQRRRRRDTH
FPICIFCCGCCHRSKCGMCCKT

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FIGURE 166

CTGTCAGGAAGGACCATCTGAAGGCTGCAATTTGTTCTTAGGGAGGCAGGTGCTGGCCTGGC
CTGGATCTTCCACCATGTTTCCTGTTGCTGCCTTTTGATAGCCTGATTGTCAACCTTCTGGGC
ATCTCCCTGACTGTCTCTTACCCTCCTTCTCGTTTTTCATCATAGTGCCAGCCATTTTTTG
AGTCTCCTTTGGTATCCGCAAACCTCTACATGAAAAGTCTGTTAAAAATCTTTGCGTGGGCTA
CCTTGAGAATGGAGCGAGGAGCCAAGGAGAAGAACCACCAGCTTTACAAGCCCTACACCAAC
GGAATCATTTGCAAAGGATCCCACTTCACTAGAAGAAGAGATCAAAGAGATTTCGTGCAAGTGG
TAGTAGTAAGGCTCTGGACAACACTCCAGAGTTCGAGCTCTCTGACATTTTCTACTTTTGCC
GGAAAGGAATGGAGACCATTATGGATGATGAGGTGACAAAGAGATTCTCAGCAGAAGAAGTGG
GAGTCTTGGAACTGCTGAGCAGAACCAATTATAACTTCCAGTACATCAGCCTTCGGCTCAC
GGTCTGTGGGGGTTAGGAGTGCTGATTTCGGTACTGCTTTCTGCTGCCGCTCAGGATAGCAC
TGGCTTTCACAGGGATTAGCCTTCTGGTGGTGGGCACAACTGTGGTGGGATACTTGCCAAAT
GGGAGGTTTAAGGAATTCATGAGTAAACATGTTCACTTAATGTGTTACCGGATCTGCGTGCG
AGCGCTGACAGCCATCATCACCTACCATGACAGGGAAAACAGACCAAGAAATGGTGGCATCT
GTGTGGCCAATCATACCTCACCGATCGATGTGATCATCTTGGCCAGCGATGGCTATTATGCC
ATGGTGGGTCAAGTGCACGGGGGACTCATGGGTGTGATTTCAGAGAGCCATGGTGAAGGCCTG
CCCACACGTCTGGTTTGAGCGCTCGGAAGTGAAGGATCGCCACCTGGTGGCTAAGAGACTGA
CTGAACATGTGCAAGATAAAAGCAAGCTGCCTATCCTCATCTTCCCAGAAGGAACCTGCATC
AATAATACATCGGTGATGATGTTCAAAAAGGGAAGTTTTGAAATTGGAGCCACAGTTTACCC
TGTTGCTATCAAGTATGACCCTCAATTTGGCGATGCCTTCTGGAACAGCAGCAAATACGGGA
TGGTGACGTACCTGCTGCGAATGATGACCAGCTGGGCCATTGTCTGCAGCGTGTGGTACCTG
CCTCCCATGACTAGAGAGGCAGATGAAGATGCTGTCCAGTTTGCGAATAGGGTGAAATCTGC
CATTGCCAGGCAGGGAGGACTTGTGGACCTGCTGTGGGATGGGGGCTGAAGAGGGAGAAGG
TGAAGGACACGTTCAAGGAGGAGCAGCAGAAGCTGTACAGCAAGATGATCGTGGGGGAACCAC
AAGGACAGGAGCCGCTCCTGAGCCTGCCTCCAGCTGGCTGGGGCCACCGTGCGGGGTGCCAA
CGGGCTCAGAGCTGGAGTTGCCGCCGCCGCCGCCACTGCTGTGTCTTTCCAGACTCCAGGG
CTCCCCGGGCTGCTCTGGATCCCAGGACTCCGGCTTTCGCCGAGCCGCAGCGGGATCCCTGT
GCACCCGGCGCAGCCTACCCTTGGTGGTCTAAACGGATGCTGCTGGGTGTTGCGACCCAGGA
CGAGATGCCTTGTTTTCTTTTACAATAAGTCGTTGGAGGAATGCCATTAAAGTGAACCTCCCCA
CCTTTGCACGCTGTGCGGGCTGAGTGGTTGGGGAGATGTGGCCATGGTCTTGTGCTAGAGAT
GGCGGTACAAGAGTCTGTTATGCAAGCCCGTGTGCCAGGGATGTGCTGGGGGCGGCCACCCG
CTCTCCAGGAAAGGCACAGCTGAGGCACTGTGGCTGGCTTCGGCCTCAACATCGCCCCAGC
CTTGGAGCTCTGCAGACATGATAGGAAGGAACTGTCTATCTGCAGGGGCTTTTCAGCAAAATG
AAGGGTTAGATTTTTATGCTGCTGCTGATGGGGTTACTAAAGGGAGGGGAAGAGGCCAGGTG
GGCCGCTGACTGGGCCATGGGGAGAACGTGTGTTTCGTAATCCAGGCTAACCCCTGAACTCCCC
ATGTGATGCGCGCTTTGTTGAATGTGTGTCTCGGTTTCCCCATCTGTAATATGAGTCGGGGG
GAATGGTGGTGATTCCCTACCTCACAGGGCTGTTGTGGGGATTAAAGTGCTGCGGGTGAGTGA
AGGACACATCACGTTCAAGTGTTCAGTGTTCAGTACAGGCCACAAAACGGGGCACGGCAGGCCTGAG
CTCAGAGCTGCTGCACTGGGCTTTGGATTTGTTCTTGTGAGTAAATAAACTGGCTGGTGAATGA

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FIGURE 167

MFLLLPFDSLIVNLLGISLTVLFTLLLVFIIVPAIFGVSFQIRKLYMKSLLKIFAWATLRME
RGAKEKNHQLYKPYTNGIIAKDPTSLEEEIKEIRRSKSSKALDNTPEFELSDIFYFCRKGME
TIMDDEVTKRFSAEELSWNLLSRTNYNFQYISLRLTVLWGLGVLIRYCFLLPLRIALFTG
ISLLVVGTTTVVGYLPNGRFKEFMKSHVHLMCYRICVRALTAITYHDRENRPNGGICVANH
TSPIDVILASDGYAMVGQVHGGLMGVIQRAMVKACPHVWFERSEVKDRHLVAKRLTEHVQ
DKSKLPILIFPEGTCINNTSVMFMKKSFEIGATVYPVAIKYDPQFGDAFWNSSKYGMVTYL
LRMMTSAIVCSVWYLPPMTREADEDAVQFANRVKSAIARQGGLVDLLWDGGLKREKVKDTF
KEEQQKLYSKMIVGNHKDRSRS

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FIGURE 168

GCCCCTCGAAACCAGGACTCCAGCACCTCTGGTCCCGCCCTCACCCGGACCCCTGGCCCTCA
CGTCTCCTCCAGGGATGGCGCTGGCGGCTTTGATGATCGCCCTCGGCAGCCTCGGCCTCCAC
ACCTGGCAGGCCCAGGCTGTTCCCACCATCCTGCCCCCTGGGCCTGGCTCCAGACACCTTTGA
CGATACCTATGTGGGTGTGTCAGAGGAGATGGAGGAGAAGGCAGCCCCCTGCTAAAGGAGG
AAATGGCCCACCATGCCCTGCTGCGGGAATCCTGGGAGGCAGCCAGGAGACCTGGGAGGAC
AAGCGTCGAGGGCTTACCTTGCCCCCTGGCTTCAAAGCCCAGAATGGAATAGCCATTATGGT
CTACACCAACTCATCGAACACCTTGTA CTGGGAGTTGAATCAGGCCGTGCGGACGGGCGGAG
GCTCCCGGGAGCTCTACATGAGGCACTTTCCCTTCAAGGCCCTGCATTTCTACCTGATCCGG
GCCCTGCAGCTGCTGCGAGGCAGTGGGGGCTGCAGCAGGGGACCTGGGGAGGTGGTGTTCGG
AGGTGTGGGCAGCCTTCGCTTTGAACCCAAGAGGCTGGGGGACTCTGTCCGCTTGGGCCAGT
TTGCCTCCAGCTCCCTGGATAAGGCAGTGGCCACAGATTTGGGGAGAAGAGGCGGGGCTGT
GTGTCTGCGCCAGGGGTGCAGCTAGGGTCACAATCTGAGGGGGCCTCCTCTCTGCCCCCTG
GAAGACTCTGCTCTTGCCCCCTGGAGAGTTCCAGCTCTCAGGGGTTGGGCCCTGAAGTCCA
ACATCTGCCACTTAGGAGCCCTGGGAACGGGTGACCTTCATATGACGAAGAGGCACCTCCAG
CAGCCTTGAGAAGCAAGAACATGGTTCCGGACCCAGCCCTAGCAGCCTTCTCCCCAACCAGG
ATGTTGGCCTGGGGAGGCCACAGCAGGGCTGAGGGA ACTCTGCTATGTGATGGGGACTTCCT
GGGACAAGCAAGGAAAGTACTGAGGCAGCCACTTGATTGAACGGTGTGCAATGTGGAGACA
TGGAGTTTTATTGAGGTAGCTACGTGATTAAATGGTATTGCAGTGTGGA

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FIGURE 169

MALAALMIALGSLGLHTWQAQAVPTILPLGLAPDTFDDTYVGCAEEMEKAAPLLKEEMAHH
ALLRESWEAAQETWEDKRRGLTLPPGFKAQNGIAIMVYTNSNTLYWELNQAVRTGGGSREL
YMRHFPPKALHFYLIRALQLLRGSGGCSRGPEVVFRGVGSLRFEPKRLGDSVRLGQFASSS
LDKAVAHRFGEKRRGCVSAPGVQLGSQSEGASSLPPWKTLLLAPGEFQLSGVGP

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FIGURE 170

GTGGCTTCATTTTCAGTGGCTGACTTCCAGAGAGCAATATGGCTGGTTCCCCAACATGCCTCA
CCCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGCTG
GTCGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTCCAAAGTAAAGCAAGTTGACTC
TATTGTCTGGACCTTCAACACAACCCCTCTTGTACCATAACAGCCAGAAGGGGGCACTATCA
TAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCCTGAAG
CTCAGCAAACTGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTCATCACT
CCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAGCCTAAAG
TCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACATGCTGCATG
GAACATGGGGAAGAGGATGTGATTTATACCTGGAAGGCCCTGGGGCAAGCAGCCAATGAGTC
CCATAATGGGTCCATCCTCCCCATCTCCTGGAGATGGGGAGAAAGTGATATGACCTTCATCT
GCGTTGCCAGGAACCCCTGTCAGCAGAACTTCTCAAGCCCCATCCTTGCCAGGAAGCTCTGT
GAAGGTGCTGCTGATGACCCAGATTCCCTCCATGGTCCTCCTGTGTCTCCTGTTGGTGCCCCCT
CCTGCTCAGTCTCTTTGTACTGGGGCTATTTCTTTGGTTTCTGAAGAGAGAGAGACAAGAAG
AGTACATTGAAGAGAAGAAGAGAGTGGACATTTGTGCGGAAACTCCTAACATATGCCCCCAT
TCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAATAGAACAATCCTAAAGGAAGA
TCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAAAGATGGAAAATCCCCACTCAC
TGCTCACGATGCCAGACACACCAAGGCTATTTGCCTATGAGAATGTTATCTAGACAGCAGTG
CACTCCCCTAAGTCTCTGCTCA

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FIGURE 171

MAGSPTCLTLIYILWQLTGSAASGPVKELVGSVGGAVTFPLKSKVKQVDSIVWTFNTTPLVT
IQPEGGTIIIVTQNRNRERVDFPDGGYSLKLSKLKKNDSGIYYVGIYSSSLQQPSTQEYVLHV
YEHLSPKPKVTMGLQSNKNGTCVTNLTCCMEHGEEDVIYTWKALGQAANESHNGSILPISWRW
GESDMTFICVARNPVSRNFSSPILARKLCEGAADDPDSSMVLLCLLLVPLLLSLFVLGLFLW
FLKRERQEYIEEKKRVDICRETPNICPHSGENTHEYDTIPHTNRTILKEDPANTVYSTVEIP
KKMENPHSLLTMPDTPRLFAYENVI

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FIGURE 172

CTGGTTCCCCAACATGCCTCACCCCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCC
TCTGGACCCGTGAAAGAGCTGGTCCGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTC
CAAAGTAAAGCAAGTTGACTCTATTGTCTGGACCTTCAACACAACCCCTCTTGTCACCATAC
AGCCAGAAGGGGGCACTATCATAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCA
GATGGAGGCTACTCCCTGAAGCTCAGCAAATGAAGAAGAATGACTCAGGGATCTACTATGT
GGGGATATACAGCTCATCACTCCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACG
AGCACCTGTCAAAGCCTAAAGTCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTG
ACCAATCTGACATGCTGCATGGAACATGGGGAAGAGGATGTGATTTATACCTGGAAGGCCCT
GGGGCAAGCAGCCAATGAGTCCCATAATGGGTCCATCCTCCCCATCTCCTGGAGATGGGGAG
AAAGTGATATGACCTTCATCTGCGTTGCCAGGAACCCTGTCAGCAGAACTTCTCAAGCCCC
ATCCTTGCCAGGAAGCTCTGTGAAGGTGCTGCTGATGACCCAGATTCCTCCATGGTCCTCCT
GTGTCTCCTGTTGGTGCCCCCTCTGCTCAGTCTCTTTGTACTGGGGCTATTTCTTTGGTTTC
TGAAGAGAGAGAGACAAGAAGAGTACATTGAAGAGAAGAAGAGAGTGGACATTTGTGGGAA
ACTCCTAACATATGCCCCCATTCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAA
TAGAACAATCCTAAAGGAAGATCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAA
AGATGGAAAATCCCCACTCACTGCTCACGATGCCAGACACACCAAGGCTATTTGCCTATGAG
AATGTTATCTAGACAGCAGTGCACTCCCCTAAGTCTCTGCTCAAAAAAAAAAAAAAAAAAAAA

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FIGURE 173

GAAAGACGTGGTCCTGACAGACAGACAATCCTATTCCCTACCAAAATGAAGATGCTGCTGCT
GCTGTGTTTGGGACTGACCCTAGTCTGTGTCCATGCAGAAGAAGCTAGTTCTACGGGAAGGA
ACTTTAATGTAGAAAAGATTAATGGGGAATGGCATACTATTATCCTGGCCTCTGACAAAAGA
GAAAAGATAGAAGAACATGGCAACTTTAGACTTTTTCTGGAGCAAATCCATGTCTTGAGAA
TTCCTTAGTTCTTAAAGTCCATACTGTAAGAGATGAAGAGTGCTCCGAATTATCTATGGTTG
CTGACAAAACAGAAAAGGCTGGTGAATATTCTGTGACGTATGATGGATTCAATACATTTACT
ATACCTAAGACAGACTATGATAACTTTCTTATGGCTCACCTCATTAACGAAAAGGATGGGGA
AACCTTCCAGCTGATGGGGCTCTATGGCCGAGAACCAGATTTGAGTTCAGACATCAAGGAAA
GGTTTGCACAACTATGTGAGGAGCATGGAATCCTTAGAGAAAATATCATTGACCTATCCAAT
GCCAATCGCTGCCTCCAGGCCCAGAAATGAAGAATGGCCTGAGCCTCCAGTGTTGAGTGGAC
ACTTCTCACCAGGACTCCACCATCATCCCTTCCTATCCATACAGCATCCCCAGTATAAATTC
TGTGATCTGCATTCCATCCTGTCTCACTGAGAAGTCCAATTCCAGTCTATCAACATGTTACC
TAGGATACCTCATCAAGAATCAAAGACTTCTTTAAATTTCTCTTTGATACACCCTTGACAAT
TTTTCATGAAATTATTCCTCTTCCTGTTCAATAAATGATTACCCTTGCACTTAA

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FIGURE 174

MKMLLLCLGLTLVCVHAEASSTGRNFNVEKINGEWHTIILASDKREKIEEHGNFRLFLEQ
IHVLENSLVLKVHTVRDEECSELSMVADKTEKAGEYSVTYDGFNTFTIPKTDYDNFLMAHLI
NEKDGETFQLMGLYGREPDLSSDIKERFAQLCEEHGILRENIIDLSNANRCLQARE

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FIGURE 175

GGCTCGAGCGTTTCTGAGCCAGGGGTGACCATGACCTGCTGCGAAGGATGGACATCCTGCAA
TGGATTGAGCCTGCTGGTTCTACTGCTGTTAGGAGTAGTTCTCAATGCGATACCTCTAATTG
TCAGCTTAGTTGAGGAAGACCAATTTTCTCAAAACCCCATCTCTTGCTTTGAGTGGTGGTTC
CCAGGAATTATAGGAGCAGGTCTGATGGCCATTCCAGCAACAACAATGTCCTTGACAGCAAG
AAAAAGAGCGTGCTGCAACAACAGAACTGGAATGTTTCTTTCATCATTTTTCAGTGTGATCA
CAGTCATTGGTGCTCTGTATTGCATGCTGATATCCATCCAGGCTCTCTTAAAGGTCTCTC
ATGTGTAATTCTCCAAGCAACAGTAATGCCAATTGTGAATTTTCATTGAAAAACATCAGTGA
CATTTCATCCAGAATCCTTCAACTTGCAGTGGTTTTTCAATGACTCTTGTGCACCTCCTACTG
GTTTCAATAAACCCACCAGTAACGACACCATGGCGAGTGGCTGGAGAGCATCTAGTTTCCAC
TTCGATTCTGAAGAAAACAAACATAGGCTTATCCACTTCTCAGTATTTTATAGGTCTATTGCT
TGTTGGAATTCTGGAGGTCCTGTTTGGGCTCAGTCAGATAGTCATCGGTTTCCTTGGCTGTC
TGTGTGGAGTCTCTAAGCGAAGAAGTCAAATTGTGTAGTTTAATGGGAATAAAATGTAAGTA
TCAGTAGTTTGAAAAAAAAAAAA

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FIGURE 176

MTCCGWTSCNGFSLVLLLLGVVLNAIPLIVSLVEEDQFSQNPISCFEWWFPGIIGAGLMA
IPATTMSLTARKRACCNRTGMFLSSFFSVITVIGALYCM LISIQALLKGPLMCNSPSNSNA
NCEFSCLKNISDIHPESFNLQWFFNDSCAPPTGFNKPTSNDTMASGWRASSFHF DSEENKHRL
IHFSVFLGLLL VGILEVLFGLSQIVIGFLGCLCGVSKRRSQIV

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FIGURE 177

GTCGAATCCAAATCACTCATTGTGAAAGCTGAGCTCACAGCCGAATAAGCCACCATGAGGCT
GTCAGTGTGTCTCCTGATGGTCTCGCTGGCCCTTTGCTGCTACCAGGCCCATGCTCTTGTCT
GCCCAGCTGTTGCTTCTGAGATCACAGTCTTCTTATTCTTAAGTGACGCTGCGGTAAACCTC
CAAGTTGCCAAACTTAATCCACCTCCAGAAGCTCTTGCAGCCAAGTTGGAAGTGAAGCACTG
CACCGATCAGATATCTTTTAAGAAACGACTCTCATTGAAAAAGTCCTGGTGGAAATAGTGAA
AAAATGTGGTGTGTGACATGTAAAAATGCTCAACCTGGTTTCCAAAGTCTTTCAACGACACC
CTGATCTTCACTAAAAATTGTAAAGGTTTCAACACGTTGCTTTAATAAATCACTTGCCCTGC

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FIGURE 178

MRLSVCLLMVSLALCCYQAHALVCPAVASEITVFLFLSDAAVNLQVAKLNPPPEALAAKLEV
KHCTDQISFKKRLSLKKSWWK

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FIGURE 179

ATCCGTTCTCTGCGCTGCCAGCTCAGGTGAGCCCTCGCCAAGGTGACCTCGCAGGACACTGG
TGAAGGAGCAGTGAGGAACCTGCAGAGTCACACAGTTGCTGACCAATTGAGCTGTGAGCCTG
GAGCAGATCCGTGGGCTGCAGACCCCCGCCCCAGTGCCTCTCCCCCTGCAGCCCTGCCCCCTC
GAACTGTGACATGGAGAGAGTGACCCTGGCCCTTCTCCTACTGGCAGGCCTGACTGCCTTGG
AAGCCAATGACCCATTTGCCAATAAAGACGATCCCTTCTACTATGACTGGAAAAACCTGCAG
CTGAGCGGACTGATCTGCGGAGGGCTCCTGGCCATTGCTGGGATCGCGGCAGTTCTGAGTGG
CAAATGCAAATACAAGAGCAGCCAGAAGCAGCACAGTCCTGTACCTGAGAAGGCCATCCCAC
TCATCACTCCAGGCTCTGCCACTACTTGCTTGAGCACAGGACTGGCCTCCAGGGATGGCCTGA
AGCCTAACACTGGCCCCCAGCACCTCCTCCCCTGGGAGGCCTTATCCTCAAGGAAGGACTTC
TCTCCAAGGGCAGGCTGTTAGGCCCTTTCTGATCAGGAGGCTTCTTTATGAATTAACTCG
CCCCACCACCCCTCA

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FIGURE 180

MERVTLALLLLAGLTALEANDPFANKDDPFYYDWKNLQLSGLICGGLLAIAGIAAVLSGKCK
YKSSQKQHSPVPEKAIPITPGSATTC

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FIGURE 181

GGAGAAGAGGTTGTGTGGGACAAGCTGCTCCCGACAGAAGGATGTCGCTGCTGAGCCTGCCC
TGGCTGGGCCTCAGACCGGTGGCAATGTCCCATGGCTACTCCTGCTGCTGGTTGTGGGCTC
CTGGCTACTCGCCCGCATCCTGGCTTGGACCTATGCCTTCTATAACAACCTGCCGCCGGCTCC
AGTGTTTCCACAGCCCCCAAACGGAACCTGGTTTTGGGGTCACCTGGGCCTGATCACTCCT
ACAGAGGAGGGCTTGAAGGACTCGACCCAGATGTGCGCCACCTATTCCCAGGGCTTTACGGT
ATGGCTGGGTCCCATCATCCCCTTCATCGTTTTATGCCACCCTGACACCATCCGGTCTATCA
CCAATGCCTCAGCTGCCATTGCACCCAAGGATAATCTCTTCATCAGGTTCTGAAGCCCTGG
CTGGGAGAAGGGATACTGCTGAGTGGCGGTGACAAGTGGAGCCGCCACCGTCGGATGCTGAC
GCCCCGCTTCCATTTCAACATCCTGAAGTCCTATATAACGATCTTCAACAAGAGTGCAAACA
TCATGCTTGACAAGTGGCAGCACCTGGCCTCAGAGGGCAGCAGTCGTCTGGACATGTTTGAG
CACATCAGCCTCATGACCTTGGACAGTCTACAGAAATGCATCTTCAGCTTTGACAGCCATTG
TCAGGAGAGGCCCAGTGAATATATTGCCACCATCTTGGAGCTCAGTGCCCTTGTAGAGAAAA
GAAGCCAGCATATCCTCCAGCACATGGACTTTCTGTATTACCTCTCCCATGACGGGCGGCGC
TTCCACAGGGCCTGCCGCTGGTGCATGACTTCACAGACGCTGTATCCGGGAGCGGCGTCTG
CACCTCCCCACTCAGGGTATTGATGATTTTTTCAAAGACAAAGCCAAGTCCAAGACTTTGG
ATTTTCATTGATGTGCTTCTGCTGAGCAAGGATGAAGATGGGAAGGCATTGTGATGAGGAT
ATAAGAGCAGAGGCTGACACCTTCATGTTTGGAGGCCATGACACCACGGCCAGTGGCCTCTC
CTGGGTCTGTACAACCTTGCGAGGCACCCAGAATACCAGGAGCGCTGCCGACAGGAGGTGC
AAGAGCTTCTGAAGGACCGGATCCTAAAGAGATTGAATGGGACGACCTGGCCCAGCTGCCC
TTCCTGACCATGTGCGTGAAGGAGAGCCTGAGGTTACATCCCCAGCTCCCTTCATCTCCCG
ATGCTGCACCCAGGACATTGTTCTCCAGATGGCCGAGTCATCCCCAAAGGCATTACCTGCC
TCATCGATATTATAGGGGTCCATCACAAACCAACTGTGTGGCCGGATCCTGAGGTCTACGAC
CCCTTCCGCTTTGACCCAGAGAACAGCAAGGGGAGGTCACCTCTGGCTTTTATTCTTTCTC
CGCAGGGCCCAGGAACATCGGGCAGGCGTTCGCCATGGCGGAGATGAAAGTGGTCCTGG
CGTTGATGCTGCTGCACTTCCGGTTCCTGCCAGACCACACTGAGCCCCGAGGAAGCTGGAA
TTGATCATGCGCGCCGAGGGCGGGCTTTGGCTGCGGGTGGAGCCCCTGAATGTAGGCTTGCA
GTGACTTTCTGACCCATCCACCTGTTTTTTTGCAGATTGTGATGAATAAAACGGTGCTGTCAA

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FIGURE 182

MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLARILAWTYAFYNNCRRLQCFPQPPKRNWFWG
HLGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIPFIVLCHPDTIRSITNASAAIAPKDNLF
IRFLKPWLGE GILLSGGDKWSRHRRLTPAFHFNILKSYITIFNKSANIMLDKWQHLASEGS
SRLDMFEHISLMTLDSLQKCIFSFD SHCQERPSEYIATILELSALVEKRSQHILQHMDFLYY
LSHDGRRFHRACRLVHDF TDAVIRERRRTLPTQGIDDFKDKAKSKTLDFIDVLLLSKDEDG
KALSDEDIRAEADTFMFGGHDTTASGLSWVLYNLARHPEYQERCQEVQELLKDRDPKEIEW
DDLAQLPFLTMCVKESLRLHPPAPFISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNPTVW
PDPEVYDPFRFDPENSKGRSPLAFIPFSAGPRNCIGQAFAMAEMKVVLALMLLHFRFLPDHT
EPRRKLELIMRAEGGLWLRVEPLNVGLQ

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FIGURE 183

CAACAGAAGCCAAGAAGGAAGCCGTCTATCTTGTGGCGATCATGTATAAGCTGGCCTCCTGC
TGTTTGCTTTTCACAGGATTCTTAAATCCTCTCTTATCTCTTCCTCTCCTTGACTCCAGGGA
AATATCCTTTCAACTCTCAGCACCTCATGAAGACGCGCGCTTAACTCCGGAGGAGCTAGAAA
GAGCTTCCCTTCTACAGATATTGCCAGAGATGCTGGGTGCAGAAAGAGGGGATATTCTCAGG
AAAGCAGACTCAAGTACCAACATTTTTAACCCAAGAGGAAATTGAGAAAGTTTCAGGATTT
CTCTGGACAAGATCCTAACATTTTACTGAGTCATCTTTTGGCCAGAATCTGGAAACCATACA
AGAAACGTGAGACTCCTGATTGCTTCTGGAAATACTGTGTCTTGAAGTGAAATAAGCATCTGT
TAGTCAGCTCAGAAACACCCATCTTAGAATATGAAAAATAACACAATGCTTGATTTGAAAC
AGTGTGGAGAAAACTAGGCAAACTACACCCTGTTTATTGTTACCTGGAAAATAAATCCTCT
ATGTTTTGCACAAAAAAAAAAAAAAAAA

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FIGURE 184

MYKLASCCLLFTGFLNPLLSLPLLDSEISFQLSAPHEDARLTPEELERASLLQILPEMLGA
ERGDILRKADSSTNIFNPRGNLRKFQDFSGQDPNILLSHLLARIWKPYKKRETPDCFWKYCV

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FIGURE 185

GAACATTTTTAGTTCCCAAGGAATGTACATCAGCCCCACGGAAGCTAGGCCACCTCTGGGAT
GGGGTTGCTGGTTTAAAACAAACGCCAGTCATCCTATATAAGGACCTGACAGCCACCAGGCA
CCACCTCCGCCAGGAAGTGCAGGCCCCACCTGTCTGCAACCCAGCTGAGGCCATGCCCTCCCC
AGGGACCGTCTGCAGCCTCCTGCTCCTCGGCATGCTCTGGCTGGACTTGGCCATGGCAGGCT
CCAGCTTCCTGAGCCCTGAACACCAGAGAGTCCAGCAGAGAAAGGAGTCGAAGAAGCCACCA
GCCAAGCTGCAGCCCCGAGCTCTAGCAGGCTGGCTCCGCCCCGGAAGATGGAGGTCAAGCAGA
AGGGGCAGAGGATGAACTGGAAGTCCGGTTCAACGCCCCCTTTGATGTTGGAATCAAGCTGT
CAGGGGTTCAGTACCAGCAGCACAGCCAGGCCCTGGGGAAGTTTCTTCAGGACATCCTCTGG
GAAGAGGCCAAAGAGGCCCCAGCCGACAAGTGATCGCCCACAAGCCTTACTCACCTCTCTCT
AAGTTTAGAAGCGCTCATCTGGCTTTTCGCTTGCTTCTGCAGCAACTCCCACGACTGTTGTA
CAAGCTCAGGAGGCGAATAAATGTTCAAAGTGTGTA

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FIGURE 186

MPSPGTVCSSLLLLGMLWLDLAMAGSSFLSPEHQRVQQRKESKKPPAKLQPRALAGWLRPEDG
GQAEGAEDLEVRFNAPFDVGIKLSGVQYQQHSQALGKFLQDILWEEAKEAPADKO

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FIGURE 187

CGGCCACAGCTGGCATGCTCTGCCTGATCGCCATCCTGCTGTATGTCTCGTCCAGTACCTC
GTGAACCCCGGGGTGCTCCGCACGGACCCCAAGATGTCAAGAATTATGAACACGTGGCTGCTGT
TCCTCCCCCTGTTCCCGGTGCAGGTGCAGACCCTGATAGTCGTGATCATCGGGATGCTCGTG
CTCCTGCTGGACTTTCTTGGCTTGGTGCACCTGGGCCAGCTGCTCATCTTCCACATCTACCT
GAGTATGTCCCCACCCCTAAGCCCCCGATCCCCCAAGGCTGGGTGGTCAGAGCTGCTCATC
TTACACCTCTACTTGAGTATGTCCCTAACCCCTGAGCCCCCACGCCTGGGGCCAGAGTCTTT
GTCCCCCGTGTGCGCATGTGTTTCAAGGTGAGCCTCTCCAGAAAGTGAGATCATGGACAAAAA
GGGCAATCACAGGAAGAAATTAAATCCATGAGGACCCAGCAGGCCAGCAAGAAGCTGAAC
TCACGCCGAGACCTGCAGGAGTGGTGCCAGGTGCTTGAAGTAACAAGTTTAAAATGTTTCA
GACAATGGAATGGAATCTATTAGGCAAGAACAGGACATTATGAAATAAGGACAGGTGGACTT
CCAAAAACACAAGTAGAAATTCTAACAATGAAATATATTACAGGCAGGTACCCACTAACCA
AACAACTGAAGCGAGAGCTGTGGTCTTGCTTGGTCTCACAGTGGGCACAGCGGTAGGCGGTC
AGTCATGTTGCTGAACGACGGAGGGTAAACTCCCCAGCCCCAAGAAAACCTGTGTTGGAAGT
AACAAACACCTCCCTGCTCCTGGCACCAGCCGTTTTGGTTCATGGTGGGCCAGCTGCAAAGCG
TCTTCCATTCTCTGGGCAGTGGTGGCCCCGAGGCTGTGGCCTCTCAGGGGGTTTCTGTGGAC
ACGGGCAGCAGAGTGTGTCCAGGCCAGCCCCAAGAATGCCCTGCTCCTGACAGCTTGGCCA
ACCCCTGGTCAGGGCAGAGGGAGTTGGGTGGGTGAGGCTCTGGGCTCACCTCCATCTCCAGA
GCATCCCCCTGCCTGCAGTTGTGGCAAGAACGCCAGCTCAGAATGAACACACCCCAACAAGA
GCCTCCTTGTTTACATAACCACAGGTTACCCTACAAACCACTGTCCCCACACAACCCTGGGGAT
GTTTTAAACACACACCTCTAACGCATATCTTACAGTCACTGTTGTCTTGCCTGAGGGTTGA
ATTTTTTTTAAATGAAAGTGCAATGAAATCACTGGATTAAATCCTACGGACACAGAGCTGAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 188

MNTWLLFLPLFPVQVQTLIVVIIIGMLVLLLDLGLVHLGQLLIFHIYLSMSPTLSPRSPQGW
VVRAAHLTPLLEYVPNPEPPTPGARVFVPRVRMCSGSASPRSEIMDKKGKSQEEIKSMRTQQ
AQQEAEELTPRPAGVVPGA

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FIGURE 189

GGAGTGCAGATGGCATCCTTCGGTTCTTCCAGACAAGCTGCAAGACGCTGACCATGGCCAAG
ATGGAGCTCTCGAAGGCCTTCTCTGGCCAGCGGACACTCCTATCTGCCATCCTCAGCATGCT
ATCACTCAGCTTCTCCACAACATCCCTGCTCAGCAACTACTGGTTTGTGGGCACACAGAAGG
TGCCCAAGCCCCCTGTGCGAGAAAGGTCTGGCAGCCAAGTGCTTTGACATGCCAGTGTCCCTG
GATGGAGATACCAACACATCCACCCAGGAGGTGGTACAATACTGGGAGACTGGGGATGA
CCGGTTCTCCTTCCGGAGCTTCCGGAGTGGCATGTGGCTATCCTGTGAGGAACTGTGGAAG
AACCAGGGGAGAGGTGCCGAAGTTTCATTGAACTTACACCACCAGCCAAGAGAGGTGAGAAA
GGACTACTGGAATTTGCCACGTTGCAAGGCCCATGTCACCCCACTCTCCGATTTGGAGGGAA
GCGGTTGATGGAGAAGGCTTCCCTCCCCTCCCCTCCCTTGGGGCTTTGTGGCAAAAATCCTA
TGGTTATCCCTGGGAACGCAGATCACCTACATCGGACTTCAATTCATCAGCTTCCTCCTGCT
ACTAACAGACTTGCTACTCACTGGGAACCCTGCCTGTGGGCTCAAACCTGAGCGCCTTTGCTG
CTGTTTCCTCTGTCCTGTCAGGTCTCCTGGGGATGGTGGCCACATGATGTATTACAAAGTC
TTCCAAGCGACTGTCAACTTGGGTCCAGAAGACTGGAGACCACATGTTTGGAAATTATGGCTG
GGCCTTCTACATGGCCTGGCTCTCCTTCACCTGCTGCATGGCGTCGGCTGTCACCACCTTCA
ACACGTACACCAGGATGGTGCTGGAGTTCAAGTGCAAGCATAGTAAGAGCTTCAAGGAAAAC
CCGAAGTGCCTACCACATCACCATCAGTGTTTCCCTCGGCGGCTGTCAAGTGCAGCCCCAC
CGTGGGTCCTTTGACCAGCTACCACCAGTATCATAATCAGCCCATCCACTCTGTCTCTGAGG
GAGTCGACTTCTACTCCGAGCTGCGGAACAAGGGATTTCAAAGAGGGGCCAGCCAGGAGCTG
AAAGAAGCAGTTAGGTCATCTGTAGAGGAAGAGCAGTGTTAGGAGTTAAGCGGGTTTGGGGA
GTAGGCTTGAGCCCTACCTTACACGTCTGCTGATTATCAACATGTGCTTAAGCCAACATCCG
TCTCTTGAGCATGGTTTTTAGAGGCTACGAATAAGGCTATGAATAAGGGTTATCTTTAAGTC
CTAAGGGATTCTGGGTGCCACTGCTCTCTTTTCTCTACAGCTCCATCTTGTTTCACCCAC
CCCACATCTCACACATCCAGAATTCCCTTCTTTACTGATAGTTTCTGTGCCAGGTTCTGGGC
TAAACCATGGAGATAAAAAGAAGAGTAAAATACACTTCCCGACCTTAAGGATCTGAAA

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FIGURE 190

MAKMELSKAFSGQRTLLSAILSMLSLSFSTTSLLSNYWFVGTQKVPKPLCEKGLAAKCFDMP
VSLDGDNTNSTQEYVQYNWETGDDRFSSFRSFRSGMWLSCEETVEEPGERCRSFIELTPPAKR
GEKGLLEFATLQGPCHPTLRFGGKRLMEKASLPSPPLGLCGKNPMVIPGNADHLHRTSIHQL
PPATNRLATHWEPCLWAQTERLCCCFLCPVRSPGDGGPHDVFTSLPSPDCQLGSRRLTTTCLE
LWLGLLHGLALLHLLHGVGCHHLQHVVHGDGAGVQVQA

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FIGURE 191

AACTGGAAGGAAAGAAAGAAAGGTCAGCTTTGGCCCAGATGTGGTTACCCCTTGGTCTCCTG
TCTTTATGTCTTTCTCCTCTTCTATTCTGTCACTCCCTCACTTAAGTCTCAGGCCTGTCA
GCAGCTCCTGTGGACATTGCCATCCCCTCTGGTAGCCTTCAGAGCAAACAGGACAACCTATG
TTATGGATGTTTCCACCAACCAGGGTAGTGGCATGGAGCACCGTAACCATCTGTGCTTCTGT
GATCTCTATGACAGAGCCACTTCTCCACCTCTGAAATGTTCCCTGCTCTGAAATCTGGCATG
AGATGGCACAGGTGACCACGCAGAAGCCACCAGAATCTTGCCTGCCCTATTCCCTCCTCCCAA
GTCTGTTCTCTTATTGTCAACCTCAGCACAACAGGCTGGCGCCAATGGCATTACAGAGAAAG
CAATCTGTGTGGCTAGTGGGCAGATTACCATGCAAGCCCCAGGAGAAATGGAGGAGCTTTGT
AGCCACCTCCCTGTGAGCCAGTATTAACATGTCCCCTTCCCCCTGCCCCGCCGTAGATTGAG
GACATTGCCCCCTGTGTGCCACCAAACCAGGACTTTCCCCTTGGCTTGGCATCCCTGGCTCT
CTCCTGGTACCCAGCAAGACGTCTGTTCCAGGGCAGTGTAGCATCTTTCAAGCTCCGTTACT
ATGGCGATGGCCATGATGTTACAATCCCACTTGCCTGAATAATCAAGTGGGAAGGGGAAGCA
GAGGGAAATGGGGCCATGTGAATGCAGCTGCTCTGTTCTCCCTACCCTGAGGAAAAACCAAA
GGGAAGCAACAGGAACTTCTGCAACTGGTTTTTATCGGAAAGATCATCCTGCCTGCAGATGC
TGTTGAAGGGGCACAAGAAATGTAGCTGGAGAAGATTGATGAAAGTGCAGGTGTGTAAGGAA
ATAGAACAGTCTGCTGGGAGTCAGACCTGGAATTCTGATTCCAAACTCTTTATTACTTTGGG
AAGTCACTCAGCCTCCCCGTAGCCATCTCCAGGGTGACGGAACCCAGTGTATTACCTGCTGG
AACCAAGGAAACTAACAATGTAGGTTACTAGTGAATACCCCAATGGTTTCTCCAATTATGCC
CATGCCACCAAAACAATAAAACAAAATTCTCTAACACTGAAA

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FIGURE 192

MWLPLGLLSLCLSPILSSPSLKSQLQQLLWTLPSPLVAFRANRTTYVMDVSTNQSGME
HRNHLCFCDLYDRATSPPLKCSLL

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FIGURE 193

GTAGCGCGTCTTGGGTCTCCCGGCTGCCGCTGCTGCCGCCGCCGCTCGGGTCTGAGGCCA
GGAGCGACGTCACCGCCATGGCAGGCATCAAAGCTTTGATTAGTTTGTCTTTTGGAGGAGCA
ATCGGACTGATGTTTTTTGATGCTTGGATGTGCCCTTCCAATATACAACAAATACTGGCCCCCT
CTTTGTTCTATTTTTTTTACATCCTTTTACCTATTCCATACTGCATAGCAAGAAGATTAGTGG
ATGATACAGATGCTATGAGTAACGCTTGTAAGGAAGTGGCATCTTTCTTACAACGGGCATT
GTCGTGTCAGCTTTTGGACTCCCTATTGTATTTGCCAGAGCACATCTGATTGAGTGGGGAGC
TTGTGCACTTGTCTCACAGGAAACACAGTCATCTTTGCAACTATACTAGGCTTTTTCTTGG
TCTTTGGAAGCAATGACGACTTCAGCTGGCAGCAGTGGTGAAAAGAAATTACTGAACTATTG
TCAAATGGACTTCCTGTCAATTGTTGGCCATTACGCACACAGGAGATGGGGCAGTTAATGC
TGAATGGTATAGCAAGCCTCTTGGGGGTATTTTAGGTGCTCCCTTCTCACTTTTATTGTAAG
CATACTATTTTACAGAGACTTGCTGAAGGATTAAGGATTTTCTCTTTTGGAAAAGCTTG
ACTGATTTTCACTTATCTATAGTATGCTTTTTTGTGGTGTCTGCTGAATTTAAATATTTAT
GTGTTTTTCTGTAGGTTGATTTTTTTTGGAAATCAATATGCAATGTTAAACACTTTTTTAA
TGTAATCATTGCAATTGGTTAGGAATTCAGAATTCGCCGGCTCTATTACTGGTCAAGTACA
TCTTTTCTCTTAAATATTATAGCCTCCATTATTACAAAAAATTATAAAAAATAAGTTTTTCA
TCAGTCAGGATGACATCACTCCCAATGTTATGCAGACATACAGACGGTTGGCATACTGTTATA
GACTGTATACTCAGTGCAAATATAGCTGCATTTATACCTCAGAGGGGCCAAGTGTTAATGCC
CATGCCCTCCGTAAAGGGTTGTTGGTTTTACTGGTAGACAGATGTTTTGTGGATTGAAAATT
ATTTTATGGAATTGCTACAGAGGAGTGCTTTTCTTCTCAATTGTTAGAAGAATTTATGTTAA
ACTTTAAGGTAAGGGTGTAACAAACATTTTTGAGATAAGGTTTTATTTATGTTTATTATTGT
TAGAGTGAGTTGCAATGTGGGAAGAAATGACATTGAAATTCAGTTTTTGAATCCTGTTTCT
ATTTATAAGTGAAATTTGTGATCTCCTATCAACCTTTTCATGTTTTACCCTGTTAAATGGAC
ATACATGGAACCACTACTGATGAGGGACAGTTGTATGTTTGCATCATATATGCCAGAAAACC
TTCTCTGCTTCTCCTTTTACTTATTTGGTATGTTGTATATATTACATAAAATAACTTTTT
CAAATATAGTTTAAATAACACTTAGAAGTGTTTACTTACCTGGAAAATAATTGCTATGCCGTA
CATTGAGAGTGCCCCCTCCCTGCAAGGCCCTGCCATGATTAACAAGTAACTTGTTAGTCTT
ACAGATAATTGATGCATTAACAGTTTAAAGTTTAGACCATGGTAATAGTAGTTCTTATTCTC
TAAGGTTATATCATATGTAATTTAAAGTATTTTTAAGACAAGTTTCCTGTATACCTCTGAA
CTGTTTTGATTTTGAAGTTTATCATGATAGATCTGCTGTTTCTTATAAAAGGCATTTGTTGT
GTGAGTTAATGCAAAGTAGCCAAGTCCAGCTATATAGCAGCTTCAGAAACATACCTGACCAA
AAAATCCCAGTAACCAGGCATGATCAATTTATAGTGGTCGTTTACATCTAATAATTATCAG
GACTTTTTTTCAGGAGTGGGTATAAAAACATTCAAGTTGGTCTGACAGTATTTTGTAAAGGA
TATTTGTTTGTATGTTTATTCAGTATACTTACATAAAAAATTATTTGCGCATCAGCCAAAAC
CAGTAATCATGACAGCTGTCTGTTGTTTTATGAAGTTTATTTCTCAAGAAAATGGGAATAAA
TTTGGGATTTGTTTCACTTTTTTACTAAAGATGCCTAAAGCCACAGGTTTTATTGCCTAACT
TAAGCCATGACTTTTAGATATGAGATGACGGGAAGCAGGACGAAATATCGGCGTGTGGCTGG
AGCCTTCCCAGTGGAGGCTGAAAGTGGCTTGTGGTATTATAATGTTTCAAGAGGAA
GGTGCAGGTACACATGAGTTAGAGAGCTGGTGAGACAGTTGGGAAGTCTTTGTGCTTGTGAT
CTACTGGACTTTTTTTTTTGCAGGAAGTGCACTCTCTGGTCCTTCCCTATTTTCTGTTCTGGA
TGTCAGTGCACTGCTACTGTTTTATCCACTTGGCCACAGACTTTTTCTAACAGCTGC
GTATTATTTCTATATACTAATTGCATTGGCAGCATTGTGTCTTTGACCTTGTATACTAGCTT
GACATAGTGCTGTCTGATTTCTAGGCTAGTTACTTGAGATATGAATTTTCCATAGAATAT
GCACTGATACAACATTACCATTTCTCTATGGAAGAAAACCTTTTGATGATGAAACAATAAG
ATTTTAAATATCTATTTTAAAAA

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FIGURE 194

MAGIKALISLSFGGAIGLMFLMLGICALPIYNKYWPLFVLFFYILSPIPYCIARRLVDDTDAM
SNACKELAIFLTGTGIVVSAFGLPIVFARAHLEWGACALVLTGNTVIFATILGFFLVFGSND
DFSWQQW

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FIGURE 195A

CCCACGCGTCCGCCACGCGTCCGCCACGCGTCCGCCACGCGTCCGCCACGCGTCCGCC
CACGCGTCCGCCACGCGTCCGGTGAAGCTCGCGCCGACACTGCCTGGTGGAGGGAAGGA
GCCCCGGCGCCTCTCGCGCTCCCCGCGCGCGGTCCGCACCTCCCCACGCGCCGCCGCCG
CCGCCCGCCGCCGCAAAGCATGAGTGAGCCCGCTCTCTGCAGCTGCCCGGGGCGGAATGG
CAGGCTGTTTTCCGCGGAGTAAAAGGTGGCGCCGTCAGTGGTCGTTTTCCAATGACGGACATT
AACCAGACTGTGAGATCCTGGGGAGTCGCGAGCCCCGAGTTTGGAGTTTTTTCCCCCACAA
CGTCACAGTCCGAAGTGCAGAGGGAAGGAAGGCGGCAGGAAGGCGAAGCTCGGGCTCCGGC
ACGTAGTTGGGAAACTTGCGGGTCTTAGAAGTCGCCTCCCCGCCTTGCCGGCCGCCCTTGCA
GCCCCGAGCCGAGCAGCAAAGTGAGACATTGTGCGCCTGCCAGATCCGCCGGCCGCGGACCG
GGGCTGCCTCGGAAACACAGAGGGGTCTTCTCGCCCTGCATATAATTAGCCTGCACACAA
AGGGAGCAGCTGAATGGAGGTTGTCACTCTCTGGAAAAGGATTTCTGACCGAGCGCTTCCAA
TGGACATTCTCCAGTCTCTCTGGAAAGATTCTCGCTAATGGATTTCTGCTGCTCGGTCTCT
GTCTATACTGGCTGCTGAGGAGGCCCTCGGGGGTGGTCTTGTGTCTGCTGGGGGCTGCTTT
CAGATGCTGCCCCGCCGCCCGAGCGGGTGCCCGCAGCTGTGCCGGTGCGAGGGGCGGCTGCT
GTACTGCGAGGCGCTCAACCTCACCAGGCGCCCCACAACCTGTCCGGCCTGCTGGGCTTGT
CCCTGCGCTACAACAGCCTCTCGGAGCTGCGCGCCGGCCAGTTCACGGGGTTAATGCAGCTC
ACGTGGCTCTATCTGGATCACAATCACATCTGCTCCGTGCAGGGGGACGCCTTTCAGAACT
GCGCTGCCGCACTGAAGTCAAGTTCACCAACAGATCACCAACTGCCCAACACCACT
TCCGGCCCATGCCAACCTGCGCAGCGTGGACCTCTCGTACAACAAGCTGCAGGCGCTCGCG
CCCGACCTCTTCCACGGGCTGCGGAAGCTCACCACGCTGCATATGCGGGCCAACGCCATCCA
GTTTGTGCCCGTGCGCATCTTCCAGGACTGCCGAGCCTCAAGTTTCTCGACATCGGATACA
ATCAGCTCAAGAGTCTGGCGCGCAACTCTTTCGCCGGCTTGTTTAAGCTCACCGAGCTGCAC
CTCGAGCACAACGACTTGGTCAAGGTGAAGTTCGCCCACTTCCCGCGCCTCATCTCCCTGCA
CTCGCTCTGCCTGCGGAGGAACAAGGTGGCCATTGTGGTCAGCTCGCTGGACTGGGTTTGGGA
ACCTGGAGAAAATGACTTGTGCGGCAACGAGATCGAGTACATGGAGCCCCATGTGTTTCGAG
ACCGTGCCGCACTGCGAGTCCCTGCGAGCTGGACTCCAACCGCCTCACCTACATCGAGCCCCG
GATCCTCAACTCTTGAAGTCCCTGACAAGCATCACCTGGCCGGGAACCTGTGGGATTGCG
GGCGCAACGTGTGTGCCCTAGCCTCGTGGCTCAGCAACTTCAGGGGCGCTACGATGGCAAC
TTGCACTGCGCCAGCCCGGAGTACGCACAGGGCGAGGACGTCTGGAGCCCGTGTACGCCTT
CCACCTGTGCGAGGATGGGGCCGAGCCCCACGAGCGGCCACCTGCTCTCGGCCGTACCAACC
GCAGTGATCTGGGGCCCCCTGCCAGCTCGGCCACCACGCTCGCGGACGGCGGGGAGGGGCGAG
CAGCAGCGCACATTCGAGCCTGCCACCGTGGCTCTTCCAGGCGGCGAGCACGCCGAGAACCG
CGTGAGATCCACAAGGTGGTCAGGGCACCATTGGCCCTCATCTTCTCCTTCCTCATCGTGG
TCCTGGTGCTCTACGTGTCTTGAAGTGTTCCTCCAGCCAGCCTCAGGCAGCTCAGACGTGC
TTTGTACGCAGCGCAGGAAGCAAAAGCAGAAACAGACCATGCATCAGATGGCTGCCATGTC
TGCCAGGAATACTACGTTGATTACAAACCGAACCACATTGAGGGAGCCCTGGTGATCATCA
ACGAGTATGGCTCGTGACCTGCCACCAGCAGCCCGCAGGGAATGCGAGGTGTGATTGTCC
CAGTGGCTCTCAACCCATGCGCTACCAATACGCCTGGGCAGCCGGGACGGGCGCGGGCA
CCAGGCTGGGGTCTCCTTGTCTGTGCTCTGATATGCTCCTTGACTGAACTTTAAGGGGATC
TCTCCCAGAGACTTGACATTTTAGCTTTATTGTGTCTTAAAAACAAAAGCGAATTTAAACAC
AACAACAAAACCCCAACCTTACGAGCAGTCTATCTTAAATTTTATATGAGAACTCC
TTCTCCCTTTTGAAGATCTGTCCATATTACGGAATCTGAGAGTGTAAAAAAGGTGGCCATAA
GACAGAGAGAGAATAATCGTGCTTTGTTTTATGCTACTCCTCCCACCCTGCCATGATTAAA
CATCATGTATGTAGAAGATCTTAAGTCCATACGCATTTTCATGAAGAACCATTGGAAGAGGA
ATCTGCAATCTGGGAGCTTAAGAGCAAATGATGACCATAGAAAGCTATGTTCTTACTTTGTG
TGTGTGTCTGTATGTTTCTGCGTGTGTGTCTTGTAGGCAAGCAAACGTTGTCTACACAAA
CGGGAATTTAGCTCACATCATTTTCATGCCCTGTGCCTCTAGCTCTGGAGATTGGTGGGGG
AGGTGGGGGGAACCGCAGGAATAAGGGAAGTGGTAGTTTTAACTAAGGTTTTGTAACT
TGAATCTTTTCTTCTCAAATTAATTATCTTAAAGCTTCAAGAACTTGCTCTGACCCCTC
TAAGCAAACTTAAGCATTTAAAGAGAATCTAATTTTTTAAAGGTGTAGCACCTTTTTTTT
TATTCTTCCACAGAGGGTGCTAATCTCATTATGCTGTGCTATCTGAAAAGAACTTAAGGCC
ACAATTCACGTCTCGTCCCTGGGCATTGTGATGGATTGACCTCCATTTGCAGTACCTTCCCA
GCTGATTAAAGTTCAGCAGTGGTATTGAGGTTTTTCGAATATTTATATAGAAAAAAGTCTT
TTCACATGACAAATGACACTCTCACACCAGTCTTAGCCCTAGTAGTTTTTTAGGTTGGACCA
GAGGAAGCAGGTTAAATGAGACCTGTCTCTGCTGCACTCAGAAAAAATAGGCAGTCCCTGA
TGCTCAGATCTTAGCCTTGATATTAATAGTTGAGACCACCTACCCACAATGCAGCCTATACT
CCCAAGACTACAAAGTTACCATCGCAAAGGAAGGTTATTCAGTAAAGGAATAGTTTTC
TCAACCATTTAAAAATATTCTTCTGAACCTCAAGAGTAGAAGAGCCCCAACCTTTTCTCT
CTGCCTTCAAGAAGGCAGACATTTGGTATGATTTAGCATCAACAACACATTTATGAGTATAT

FIGURE 195B

GTAAGTAATCAGAGGGGCAAATGCCACTTGTTATTCCTCCCAAGTTTTCCAAGCAAGTACAC
ACAGATCTCTGGTAGGATTAGGGGCCACTTGTGTTTCCGGCTTATTTTAGTCGACTTGTCAG
CAAGTTTGATGCCTAGTCTATCTGACATGGCCCAGTAGAACAGGGCATTGATGGATCACATG
AGATGGTAGAAGGAACATCATCACATACCCCTCTCACAGAGAAAATTATCAAAGAACCAGAA
ATTATATCTGTTTTGGAGCAAGAGTGTCTAATGTTTCAGGGTAGTCAAATAAACATAAAT
TATCTCCTCTAGATGAGTGGCGATGTTGGCTGATTTGGGTCTGCCATTGACAGAATGTCAA
TAAAAAGGAATTAGCTAGAATATGACCATTAAATGTGCTTCTGAAATATATTTTGAGATAGG
TTTAGAATGTCA

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FIGURE 196

MDFLLLGLCLYWLLRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEAPH
NLSGLLGLSLRYNLSSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTLSSNQ
ITQLPNTTFRPMPNLRSDLSYNKLQALAPDLFHGLRKLTTLHMRANAIQFVPVRIFQDCRS
LKFLDIGYNQLKSLARNSFAGLFKLTELHLEHNDLVKVNFAHFPRLISLHSLCLRRNKVAIV
VSSLDWVWNLEKMDLSGNEIEYMEPHVFETVPHLQSLQLDSNRLTYIEPRILNSWKSLSIT
LAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDVYAFHLCEDGAEPTSG
HLLSAVTNRSDLGPPASSATTADGGEGQHDGTFEPATVALPGGEHAENAVQIHKVVTGTMA
LIFSFLIVVLVLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQMAAMSAQEYYVDYKPNH
IEGALVIINEYGSCTCHQQPARECEV

FIGURE 197

GTGCAAGGAGCCGAGGCGAGATGGGCGTCTTGGGCCGGGTCCTGCTGTGGCTGCAGCTCTGC
GCACTGACCCAGGCGGTCTCCAAACTCTGGGTCCCCAACACGGACTTCGACGTGCGAGCCAA
CTGGAGCCAGAACCGGACCCCGTGCGCCGGCGGCGCCGTTGAGTTCCCGGCGGACAAGATGG
TGTCAGTCCTGGTGCAAGAAGGTCACGCCGTCTCAGACATGCTCCTGCCGCTGGATGGGGAA
CTCGTCCTGGCTTCAGGAGCCGGATTGCGCGTCTCAGACGTGGGCTCGCACCTGGACTGTGG
CGCGGGCGAACCTGCCGTCTTCCGCGACTCTGACCGCTTCTCCTGGCATGACCCGCACCTGT
GGCGCTCTGGGGACGAGGCACCTGGCCTCTTCTTCGTGGACGCCGAGCGCGTGCCCTGCCGC
CACGACGACGTCTTCTTTCCGCCTAGTGCCTCCTTCCGCGTGGGGCTCGGCCCTGGCGCTAG
CCCCGTGCGTGTCGCGAGCATCTCGGCTCTGGGCCGGACGTTACGCGCGACGAGGACCTGG
CTGTTTTCTTGGCGTCCCGCGCGGGCCGCCTACGCTTCCACGGGCCGGGCGCGCTTGAGCGTG
GGCCCCGAGGACTGCGCGGACCCGTGCGGCTGCGTCTGCGGCAACGCGGAGGCGCAGCCGTG
GATCTGCGCGGCCCTGCTCCAGCCCCT

FIGURE 198

MGVLGRVLLWLQLCALTQAVSKLWVPNTDFDVAANWSQNRTPCAGGAVEFPADKMVSVLVQE
GHAVSDMLLPLDGELVLASGAGFGVSDVGSHLDCGAGEPAVFRDSDRFSWHDPHLWRSGDEA
PGLFFVDAERVPCRHDDVFFPPSASFVGLGPGASPVRVRSISALGRTFTRDEDLAVFLASR
AGRLRFHGGALSVGPEDCADPSGCVCGNAEAQPWICAALLQP

[illegible]

FIGURE 200

MGPVKQLKRMFEPTRLIATIMVLLCFALTLCSAFWWHNKGLALIFCILQSLALTWYSLSFIP
FARDAVKKCFVCLA

FIGURE 201

TTGAGCGCAGGTGAGCTCCTGCGCGTTCCGGGGGCGTTCTCCAGTCACCCCTCCCGCCGTTA
CCCGCGGCGCGCCCGAGGGAGTCTCCTCCAGACCCCTCCCTCCCGTTGCTCCAAACTAATACG
GACTGAACGGATCGCTGCGAGGGTGGGAGAGAAAATTAGGGGGAGAAAGGACAGAGAGAGCA
ACTACCATCCATAGCCAGATAGATTATCTTACACTGAACTGATCAAGTACTTTGAAAATGAC
TTCGAAATTTATCTTGGTGTCTTCATACTTGCTGCACTGAGTCTTTCAACCACCTTTTCTC
TCCAACTAGACCAGCAAAAGGTTCTACTAGTTTCTTTTGATGGATTCCGTGGGATTACTTA
TATAAAGTTCCAACGCCCCATTTTCATTATATTATGAAATATGGTGTTCACGTGAAGCAAGT
TACTAATGTTTTTATTACAAAACCTACCCTAACCATTATACTTTGGTAACCTGGCCTCTTTG
CAGAGAATCATGGGATTGTTGCAAAATGATATGTTTGATCCTATTTCGGAACAAATCTTTCTCC
TTGGATCACATGAATATTTATGATTCCAAGTTTGGGAAGAAGCGACACCAATATGGATCAC
AAACCAGAGGGCAGGACATACTAGTGGTGCAGCCATGTGGCCCGGAACAGATGTAAAAATAC
ATAAGCGCTTTCCTACTCATTACATGCCTTACAATGAGTCAGTTTCATTTGAAGATAGAGTT
GCCAAAATGTTGAATGGTTTACGTCAAAGAGCCCATAAATCTTGGTCTTCTCTATTGGGA
AGACCCTGATGACATGGGCCACCATTTGGGACCTGACAGTCCGCTCATGGGGCCTGTCAATT
CAGATATTGACAAGAAGTTAGGATATCTCATACAAATGCTGAAAAGGCAAAGTTGTGGAAC
ACTCTGAACCTAATCATCACAAGTGATCATGGAATGACGCAGTGCTCTGAGGAAAGGTTAAT
AGAACTTGACCAGTACCTGGATAAAGACCACTATAACCCTGATTGATCAATCTCCAGTAGCAG
CCATCTTGCCAAAAGAAGGTAAATTTGATGAAGTCTATGAAGCACTAACTCACGCTCATCCT
AATCTTACTGTTTACAAAAAGAAGACGTTCCAGAAAGGTGGCATTACAAATACAACAGTCG
AATTCAACCAATCATAGCAGTGGCTGATGAAGGGTGGCACATTTTACAGAATAAGTCAGATG
ACTTTCTGTAGGCAACCACGGTTACGATAATGCGTTAGCAGATATGCATCCAATATTTTGA
GCCCATGGTCTGCTTCAGAAAGAATTTCTCAAAGAAGCCATGAACTCCACAGATTTGTA
CCCCTACTATGCCACCTCCTCAATATCACTGCCATGCCACACAATGGATCATTCTGGAATG
TCCAGGATCTGCTCAATTCAGCAATGCCAAGGGTGGTCCCTTATACACAGAGTACTATACTC
CTCCCTGGTAGTGTTAAACCAGCAGAATATGACCAAGAGGGGTCTATACCCTTATTTTCATAGG
GGTCTCTCTTGGCAGCATTATAGTGATTGTATTTTGTAAATTTTCATTAAGCATTTAATTC
ACAGTCAAATACCTGCCTTACAAGATATGCATGCTGAAATAGCTCAACCATTATTACAAGCC
TAATGTGTACTTTGAAGTGGATTTGCATATTGAAGTGGAGATTCCATAATTATGTCAGTGT
AAAGGTTTCAAATCTGGGAAACCAGTTCCAAACATCTGCAGAAACCATTAAAGCAGTTACAT
ATTTAGGTATAC
CTGCAAAGGAATAAAGATGTGAGAGTATGTCTCCATTGTTCACTGTAGCATAGGGATAGATA
AGATCCTGCTTTATTTGGACTTGGCGCAGATAATGTATATATTTAGCAACTTTGCACTATGT
AAAGTACCTTATATATTGCACTTTAAATTTCTCTCCTGATGGGTACTTTAATTTGAAATGCA
CTTTATGGACAGTTATGTCTTATAACTTGATTGAAAATGACAACCTTTTGCACCCATGTCAC
AGAATACTTGTTACGCATTGTTCAAACCTGAAGGAAATTTCTAATAATCCCGAATAATGAACA
TAGAAATCTATCTCCATAAATTGAGAGAAGAAGAAGGTGATAAGTGTGAAAATTAATGTG
ATAACCTTTGAACCTTGAATTTTGGAGATGTATTCCCAACAGCAGAATGCAACTGTGGGCAT
TTCTTGCTTATTTCTTTCCAGAGAACGTGGTTTTCATTTATTTTCCCTCAAAAGAGAGTC
AAATACTGACAGATTGCTTCTAAATATATTGTTTCTGTCTATAAAATTAATTGTGATTTCTGA
TGAGTCATATTACTGTGATTTTCATAATAATGAAGACACCATGAATATACTTTTCTTCTATA
TAGTTCAAGCAATGGCCTGAATAGAAAGCAACCAGGCACCATCTCAGCAATGTTTCTCTTGT
TGTAATTATTTGCTCCTTTGAAAATTAATCACTATTAATTACATTAATAATCAAAATGGAT
AAAAAAAAAAAAAAAAAAAA

FIGURE 202

MTSKFILVSFILAALSLSTTFSLQLDQQKVLLVSFDGFRWDYLYKVPTPHFHYIMKYGVHVK
QVTNVFITKTYPNHYTLVTGLFAENHGIVANDMFDPIRNKSFSLDHMNIYDSKFWEETPIW
ITNQ RAGHTSGAAMWPGTDVKIHKRFPTHYMPYNESVSFEDRVAKIVEWFTSKEPINLGLLY
WEDPDDMGHHLGPDSPLMGPVISDIDKKLGYLIQMLKKAKLWNTLNLIITSDHGMTQCSEER
LIELDQYLDKDHYTELIDQSPVAAAILPKEGKFDEVYEALTHAHPNLTVYKKEDVPERWHYKYN
SRIQPIIAVADEGWHILQNKSDDFLLGNHGYDNALADMHPIFLAHGPAFRKNFSKEAMNSTD
LYPLLCHLLNITAMPHNGSFWNVQDLLNSAMPRVVPYTQSTILLPGSVKPAEYDQEGSYPYF
IGVSLGSIIVIVFFVIFIKHLIHSQIPALQDMHAEIAQPLLQA

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FIGURE 203

GGATTTTGTGATCCGCGATTTCGCTCCACGGGCGGGACCTTTGTAAGTGC GGGAGGCCCAG
GACAGGCCCACCCTGCGGGGCGGGAGGCAGCCGGGGTGAGGGAGGTGAAGAAACCAAGACGC
AGAGAGGCCAAGCCCCTTGCCTTGGGTCACACAGCCAAAGGAGGCAGAGCCAGAACTCACAA
CCAGATCCAGAGGCAACAGGGACATGGCCACCTGGGACGAAAAGGCAGTCACCCGCAGGGCC
AAGGTGGCTCCCGCTGAGAGGATGAGCAAGTTCTTAAGGCACTTCACGGTCGTGGGAGACGA
CTACCATGCCTGGAACATCAACTACAAGAAATGGGAGAATGAAGAGGAGGAGGAGGAGGAGG
AGCAGCCACCACCCACACCAGTCTCAGGCGAGGAAGGCAGAGCTGCAGCCCCTGACGTTGCC
CCTGCCCCCTGGCCCCGCACCCAGGGCCCCCCTTGACTTCAGGGGCATGTTGAGGAACTGTT
CAGCTCCACAGGTTTCAGGTCATCATCATCTGCTTGGTGGTTCTGGATGCCCTCCTGGTGC
TTGCTGAGCTCATCCTGGACCTGAAGATCATCCAGCCCGACAAGAATAACTATGCTGCCATG
GTATTCCACTACATGAGCATCACCATCTTGGTCTTTTTTATGATGGAGATCATCTTTAAATT
ATTTGTCTTCCGCCTGAGTTCTTTTACCACAAGTTTGAGATCCTGGATGCCCGTCGTGGTGG
TGGTCTCATTATCCTGGACATTGTCCTCCTGTTCCAGGAGCACCAGTTTGAGGCTCTGGGC
CTGCTGATTCTGCTCCGGCTGTGGCGGGTGGCCCGGATCATCAATGGGATTATCATCTCAGT
TAAGACACGTTTCAGAACGGCAACTCTTAAGGTAAAAACAGATGAATGTACAATTGGCCGCCA
AGATTCAACACCTTGAGTTCAGCTGCTCTGAGAAGCCCCTGGACTTGATGAGTTTGCTGTATC
AACCTGTAAGGAGAAGCTCTCTCCGGATGGCTATGGGAATGAAAGAATCCGACTTCTACTCT
CACACAGCCACCGTGAAAGTCCTGGAGTAAAATGTGCTGTGTACAGAAGAGAGAGAAGGAAG
CAGGCTGGCATGTTCACTGGGCTGGTGTACGACAGAGAACCTGACAGTCACTGGCCAGTTA
TCACTTCAGATTACAAATCACACAGAGCATCTGCCTGTTTTCAATCACAAGAGAACAAAACC
AAAATCTATAAAGATATTCTGAAAATATGACAGAATTTGACAAATAAAAGCATAAACGTGTA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 204

MATWDEKAVTRRAKVAPAERMSKFLRHFTVVGDDYHAWNINYYKKWENEEEEEEEEQPPPTPV
SGEEGRAAAPDVAPAPGPAPRAPLDFRGMLRKLFSSHRFQVIIICLVVLDALLVLAELIDL
KIIQPDKNYAAMVFHYMSITILVFFMMEIIFKLFVFRLLSSFTTSLRSWMPVVVVVSFILD
VLLFQEHQFEALGLLILLRLWRVARIINGIIISVKTRSERQLRLKQMNVQLAAKIQHLEFS
CSEKPLD

FIGURE 206

MLCLCLYVPVIGEAQTEFQYFESKGLPAELKSIFKLSVFIPSQEFSTYRQWKQKIVQAGDKD
LDGQLDFEEFVHYLQDHEKKLRLVFKILDKKNDGRIDAQEIMQSLRDLGVKISEQQAEEKILK
SMDKNGTMTIDWNEWRDYHLLHPVENIPEIILYWKHSTIFDVGENLTVPDEFTVEERQTGMW
WRHLVAGGGAGAVSRTCTAPLDRLKVLMOVHASRSNNMGIVGGFTQMIREGGARSLWRGNGI
NVLKIAPESAIKFMAYEQIKRLVGSDQETLRIHERLVAGSLAGAIQAQSSIYPMEVLKTRMAL
RKTGQYSGMLDCARRILAREGVAAFYKGYVPNMLGIIPYAGIDLAVYETLKNWLQHYAVNS
ADPGVFVLLACGTMSSTCGQLASYPLALVRTRMQAQASIEGAPEVTMSSLFKHILRTEGAFG
LYRGLAPNFMKVIPAVSISYVVYENLKITLGVQSR

FIGURE 207

GGAAGGCAGCGGCAGCTCCACTCAGCCAGTACCCAGATACGCTGGGAACCTTCCCCAGCCAT
GGCTTCCCTGGGGCAGATCCTCTTCTGGAGCATAATTAGCATCATCATTATTCTGGCTGGAG
CAATTGCACTCATCATTGGCTTTGGTATTTTCAGGGAGACACTCCATCACAGTCACTACTGTC
GCCTCAGCTGGGAACATTGGGGAGGATGGAATCCTGAGCTGCACTTTTGAACCTGACATCAA
ACTTTCTGATATCGTGATACAATGGCTGAAGGAAGGTGTTTTAGGCTTGGTCCATGAGTTCA
AAGAAGGCCAAAGATGAGCTGTCCGAGCAGGATGAAATGTTTCAGAGGCCGGACAGCAGTGTTT
GCTGATCAAGTGATAGTTGGCAATGCCTCTTTGCGGCTGAAAAACGTGCAACTCACAGATGC
TGGCACCTACAAATGTTATATCATCACTTCTAAAGGCAAGGGGAATGCTAACCTTGAGTATA
AAACTGGAGCCTTCAGCATGCCGGAAGTGAATGTGGACTATAATGCCAGCTCAGAGACCTTG
CGGTGTGAGGCTCCCCGATGGTTCCCCCAGCCCACAGTGGTCTGGGCATCCCAAGTTGACCA
GGGAGCCAACTTCTCGGAAGTCTCCAATACCAGCTTTGAGCTGAACTCTGAGAATGTGACCA
TGAAGGTTGTGTCTGTGCTCTACAATGTTACGATCAACAACACATACTCCTGTATGATTGAA
AATGACATTGCCAAAGCAACAGGGGATATCAAAGTGACAGAATCGGAGATCAAAGGCGGAG
TCACCTACAGCTGCTAAACTCAAAGGCTTCTGTGTGTCTCTTCTTTCTTTGCCATCAGCT
GGGCACTTCTGCCTCTCAGCCCTTACCTGATGCTAAAATAATGTGCCTTGGCCACAAAAAAG
CATGCAAAGTCATTGTTACAACAGGGATCTACAGAACTATTTACCACCAGATATGACCTAG
TTTTATATTTCTGGGAGGAAATGAATTCATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCA
AGAAACAAAAAGAAGCCAAAAGCAGAAGGCTCCAATATGAACAAGATAAATCTATCTTCAAA
GACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAAGAGTGATAAG
TAAATGCACGTGGAGACAAGTGCATCCCCAGATCTCAGGGACCTCCCCCTGCCTGTCACCT
GGGGAGTGAGAGGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTATGTTATATGTGCTG
TAATGTTGCTCTGAGGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCA
CAAATTAAGCTGTAGTATGTACCCTAAGACGCTGCTAATTGACTGCCACTTCGCAACTCAGG
GGCGGCTGCATTTTAGTAATGGGTCAAATGATTCACTTTTTATGATGCTTCCAAAGGTGCCT
TGGCTTCTCTTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATAATTTTAGCATAA
ACAGAGCAGTCGGGGACACCGATTTTATAAATAAACTGAGCACCTTCTTTTAAACAAAAAA
AA

FIGURE 208

MASLGQILFWSIISIIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDI
KLSDIVIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTD
AGTYKCYIITSKGKGNANLEYKTGAFSMPEVNVNDYNASSETLRCEAPRWFPPQPTVVWASQVD
QGANFSEVSNTSFELNSENVTMKVVSVLNVNTINNTYSCMIENDIAKATGDIKVTSEIKRR
SHLQLLNSKASLCVSSFFAISWALLPLSPYLMLK

FIGURE 209

[illegible]

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FIGURE 210

MAASLGQVLALVLVAALWGGTQPLLKRASAGLQRVHEPTWAQQLQEMKTLFLNTEYLMPFL
LNQCGSLLYLTLASTDLTAVPICNSLAIIFTLIVGKALGEDIGGKRKLDYCECGTQLCGS
RHTCVSSFPEPISPEWVRTRPFPILPFPLQLFCFLVAIRVPFPWTVWRKTEAGVWD

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FIGURE 211

CTTCTGTAGGACAGTCACCAGGCCAGATCCAGAAGCCTCTCTAGGCTCCAGCTTTCTCTGTG
GAAGATGACAGCAATTATAGCAGGACCCTGCCAGGCTGTGCGAAAAGATTCCGCAATAAAACT
TTGCCAGTGGGAAGTACCTAGTGAAACGGCCTAAGATGCCACTTCTTCTCATGTCCCAGGCT
TGAGGCCCTGTGGTCCCCATCCTTGGGAGAAGTCAGCTCCAGCACCATGAAGGGCATCCTCG
TTGCTGGTATCACTGCAGTGCTTGTTGCAGCTGTAGAATCTCTGAGCTGCGTGCAGTGTAAT
TCATGGGAAAAATCCTGTGTCAACAGCATTGCCTCTGAATGTCCCTCACATGCCAACACCAG
CTGTATCAGCTCCTCAGCCAGCTCCTCTCTAGAGACACCAGTCAGATTATACCAGAATATGT
TCTGCTCAGCGGAGAACTGCAGTGAGGAGACACACATTACAGCCTTCACTGTCCACGTGTCT
GCTGAAGAACACTTTTCATTTTGTAAGCCAGTGCTGCCAAGGAAAGGAATGCAGCAACACCAG
CGATGCCCTGGACCCTCCCCTGAAGAACGTGTCCAGCAACGCAGAGTGCCCTGCTTGTTATG
AATCTAATGGAACCTCCTGTGCGTGGGAAGCCCTGGAAATGCTATGAAGAAGAACAGTGTTGTC
TTTCTAGTTGCAGAACTTAAGAATGACATTGAGTCTAAGAGTCTCGTGCTGAAAGGCTGTTT
CAACGTCAGTAACGCCACCTGTCAGTTCCTGTCTGGTGAAAACAAGACTCTTGGAGGAGTCA
TCTTTCGAAAGTTTGAGTGTGCAAATGTAAACAGCTTAACCCCCACGTCTGCACCAACCACT
TCCCACAACGTGGGCTCCAAAGCTTCCCTCTACCTCTTGGCCCTTGCCAGCCTCCTTCTTCG
GGGACTGCTGCCCCGAGGTCTGGGGCTGCACTTTGCCCAGCACCCCATTTCTGCTTCTCTG
AGGTCCAGAGCACCCCTGCGGTGCTGACACCCTCTTCCCTGCTCTGCCCCGTTTAACTGC
CCAGTAAGTGGGAGTCACAGGTCTCCAGGCAATGCCGACAGCTGCCTTGTTCTTCATTATTA
AAGCACTGGTTTCATTCACTGCCAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 212

MKGILVAGITAVLVAAVESLSCVQCNSWEKSCVNSIASECPSHANTSCISSSASSSLETPVR
LYQNMFCSAENCSEETHITAFTVHVSAEEHFHFVSQCCQGKECSNTSDALDPPLKNVSSNAE
CPACYESNGTSCRGKPWKCYEEEQCVFLVAELKNDIESKSLVLKGCSNVSNATCQFLSGENK
TLGGVIFRKFEKANVNSLTPTSAPTTSNVGSKASLYLLALASLLLRGLLP

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FIGURE 213

GGCCTCGGTTCAAACGACCCGGTGGGTCTACAGCGGAAGGGAGGGAGCGAAGGTAGGAGGCA
GGGCTTGCCCTCACTGGCCACCCTCCCAACCCCAAGAGCCCAGCCCCATGGTCCCCGCCGCCG
GCGCGCTGCTGTGGGTCTGCTGCTGAATCTGGGTCCCCGGGCGGCGGGGGCCCCAAGGCCTG
ACCCAGACTCCGACCGAAATGCAGCGGGTCAGTTTACGCTTTGGGGGCCCCATGACCCGCAG
CTACCGGAGCACCGCCCGGACTGGTCTTCCCCGGAAGACAAGGATAATCCTAGAGGACGAGA
ATGATGCCATGGCCGACGCCGACCGCTGGCTGGACCAGCGGCTGCCGAGCTCTTGGCCGCC
ACGGTGTCCACCGGCTTTAGCCGGTCGTCCGCCATTAACGAGGAGGATGGGTCTTCAGAAGA
GGGGGTGTGATTAATGCCGGAAGGATAGCACCAGCAGAGAGCTTCCAGTGCGACTCCCA
ATACAGCGGGGAGTTCCAGCACGAGGTTTATAGCCAATAGTCAGGAGCCTGAAATCAGGCTG
ACTTCAAGCCTGCCGCGCTCCCCGGGAGGTCTACTGAGGACCTGCCAGGCTCGCAGGCCAC
CCTGAGCCAGTGGTCCACACCTGGGTCTACCCGAGCCGGTGGCCGTCACCCCTACCCACAG
CCATGCCATCTCCTGAGGATCTGCGGCTGGTGCTGATGCCCTGGGGCCCGTGGCACTGCCAC
TGCAAGTCGGGCACCATGAGCCGAGCCGGTCTGGGAAGCTGCACGGCCTTTCCGGGCGCCT
TCGAGTTGGGGCGCTGAGCCAGCTCCGCACGGAGCACAAGCCTTGACCTATCAACAATGTC
CCTGCAACCGACTTCGGGAAGAGTGCCCCCTGGACACAAGTCTCTGTACTGACACCAACTGT
GCCTCTCAGAGCACCACCAGTACCAGGACCACCACTACCCCTTCCCCACCATCCACCTCAG
AAGCAGTCCCAGCCTGCCACCCGCCAGCCCCTGCCAGCCCTGGCTTTTGGAAACGGGTCA
GGATTGGCCTGGAGGATATTTGGAATAGCCTCTCTTCAGTGTTACAGAGATGCAACCAATA
GACAGAAACCAGAGGTAAATGGCCACTTCATCCACATGAGGAGATGTCAGTATCTCAACCTCT
CTTGCCCTTTCAATCCTAGCACCCACTAGATATTTTGTACAGAAAAACAACTGGAAAA
CACAA

FIGURE 214

MVPAAGALLWVLLLNLGPRAAGAQGLTQTPTEMQRVSLRFGGPMTRSYRSTARTGLPRKTRI
ILEDENDAMADADRLAGPAAAELLAATVSTGFSRSSAINEEDGSSEEGVVINAGKDSTSREL
PSATPNTAGSSSTRFIANSQEPEIRLTSSLPRSPGRSTEDLPGSQATLSQWSTPGSTPSRWP
SPSPTAMPSPEDLRLVLMWPWGPWHCHCKSGTMSRSRSGKLHGLSGRLRVGALSQLRTEHKPC
TYQQCPCNRLREECPLDTSLCDTNCASQSTTSTRTTTTPFPTIHLRSSPSLPPASPCPALA
FWKRVRIGLEDIWNSLSSVFTEMQPIDRNQR

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FIGURE 215

CCCGGGTCGACCCACGCGTCCGGGGAGAAAGGATGGCCGGCCTGGCGGCGCGGTGGTCTCTG
CTAGCTGGGGCAGCGGCGCTGGCGAGCGGCTCCCAGGGCGACCGTGAGCCGGTGTACCGCGA
CTGCGTACTGCAGTGCGAAGAGCAGAACTGCTCTGGGGGCGCTCTGAATCACTTCCGCTCCC
GCCAGCCAATCTACATGAGTCTAGCAGGCTGGACCTGTCTGGGACGACTGTAAGTATGAGTGT
ATGTGGGTACCGTTGGGCTCTACCTCCAGGAAGGTCAAAAGTGCCTCAGTTCATGGCAA
GTGGCCCTTCTCCCGGTTCTGTCTTTCAAGAGCCGGCATCGGCCGTGGCCTCGTTTCTCA
ATGGCCTGGCCAGCCTGGTGATGCTCTGCCGCTACCGCACCTTCGTGCCAGCCTCCTCCCC
ATGTACCACACCTGTGTGGCCTTCGCCTGGGTGTCCCTCAATGCATGGTTCTGGTCCACAGT
CTTCCACACCAGGGACACTGACCTCACAGAGAAAATGGACTACTTCTGTGCCTCCACTGTCA
TCCTAACTCAATCTACCTGTGCTGCGTCAGGACCGTGGGGCTGCAGCACCCAGCTGTGGTC
AGTGCCTTCCGGGCTCTCCTGCTGCTCATGCTGACCGTGACGTCTCCTACCTGAGCCTCAT
CCGCTTCGACTATGGCTACAACCTGGTGGCCAACGTGGCTATTGGCCTGGTCAACGTGGTGT
GGTGGCTGGCCTGGTGCCTGTGGAACCAGCGGCGGCTGCCTCACGTGCGCAAGTGCCTGGTG
GTGGTCTTGCTGCTGCAGGGGCTGTCCCTGCTCGAGCTGCTTGACTTCCCACCGCTCTTCTG
GGTCTTGATGCCCATGCCATCTGGCACATCAGCACCATCCCTGTCCACGTCTCTTTTTCA
GCTTTCTGGAAGATGACAGCCTGTACCTGCTGAAGGAATCAGAGGACAAGTTCAAGCTGGAC
TGAAGACCTTGGAGCGAGTCTGCCCCAGTGGGGATCCTGCCCCCGCCCTGCTGGCCTCCCTT
CTCCCCCTCAACCCTTGAGATGATTTTCTCTTTTCAACTTCTTGAACCTGGACATGAAGGATG
TGGGCCCAGAATCATGTGGCCAGCCCACCCCTGTTGGCCCTCACCAGCCTTGGAGTCTGTT
CTAGGGAAGGCCTCCCAGCATCTGGGACTCGAGAGTGGGCAGCCCTCTACCTCCTGGAGCT
GAACTGGGGTGGAACTGAGTGTGTTCTTAGCTCTACCGGGAGGACAGCTGCCTGTTTCTCTC
CCACCAGCCTCTCCCCACATCCCCAGCTGCCTGGCTGGGTCTGAAGCCCTCTGTCTACCT
GGGAGACCAGGGACCACAGGCCTTAGGGATACAGGGGGTCCCCTTCTGTTACCACCCCCAC
CCTCCTCCAGGACACCACTAGGTGGTGTGATGCTTGTCTTTGGCCAGCCAAGGTTACAG
GCGATTCTCCCCATGGGATCTTGAGGGACCAAGCTGCTGGGATTGGGAAGGAGTTTACCCT
GACCGTTGCCCTAGCCAGGTTCCCAGGAGGCCTCACCATACTCCCTTTCAGGGCCAGGGCTC
CAGCAAGCCCAGGGCAAGGATCCTGTGCTGCTGTCTGGTTGAGAGCCTGCCACCGTGTGTG
GGAGTGTGGGCCAGGCTGAGTGATAGGTGACAGGGCCGTGAGCATGGGCCTGGGTGTGTGT
GAGCTCAGGCCTAGGTGCGCAGTGTGGAGACGGGTGTTGTCTGGGGAAGAGGTGTGGCTTCAA
AGTGTGTGTGTGCAGGGGGTGGGTGTGTAGCGTGGGTAGGGGAACGTGTGTGCGCGTGTCT
GGTGGGCATGTGAGATGAGTGAAGTGCCTGTAATGTGTCCACAGTTGAGAGGTTGGAGCAGG
ATGAGGGAATCCTGTACCATCAATAACTTGTGGAGCGCCAGCTCTGCCAAGACGCCA
CCTGGGCGGACAGCCAGGAGCTCTCCATGGCCAGGCTGCCTGTGTGCATGTTCCCTGTCTGG
TGCCCCTTTGCCCGCCTCCTGCAAACCTCACAGGGTCCCCACACAACAGTGCCTTCCAGAAG
CAGCCCCCTCGGAGGCAGAGGAAGGAAAATGGGGATGGCTGGGGCTCTCTCCATCCTCTTTT
CTCCTTGCCCTTCGCATGGCTGGCCTTCCCCCTCAAAACCTCCATTCCCCTGCTGCCAGCCCC
TTTGCCATAGCCTGATTTTGGGGAGGAGGAAGGGGCGATTTGAGGGAGAAGGGGAGAAAGCT
TATGGCTGGGTCTGGTTTCTTCCCTTCCCAGAGGGTCTTACTGTTCCAGGGTGGCCCCAGGG
CAGGCAGGGGCCACACTATGCCTGTGCCCTGGTAAAGGTGACCCCTGCCATTTACCAGCAGC
CCTGGCATGTTCTTCCCCACAGGAATAGAATGGAGGGAGCTCCAGAACTTTCCATCCCAA
AGGCAGTCTCCGTGGTTGAAGCAGACTGGATTTTGTCTGTGCCCTGACCCCTGTCCCTCT
TTGAGGGAGGGGAGCTATGCTAGGACTCCAACCTCAGGGACTCGGGTGGCCTGCGCTAGCTT
CTTTTGATACTGAAAACCTTTAAGGTGGGAGGGTGGCAAGGGATGTGCTTAATAAATCAATT
CCAAGCCTCAAAAAAAAAAAAAAAAAA

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FIGURE 216

MAGLAARLVLLAGAAALASGSQGDREPVYRDCVLQCEEQNCSGGALNHFRSRQPIYMSLAGW
TCRDDCKYECMWVTVGLYLQEGHKVPQFHGKWPF SRFLFFQEPASAVASFLNGLASLVMLCR
YRTFVPASSPMYHTCVAFWVSLNAFWSTVFHTRDTDLTEKMDYFCASTVILHSIYLCCVR
TVGLQHPAVVSAFRALLLLMLTVHVSYSLSLIRFDYGYNLVANVAIGLVNVVWWLAWCLWNQR
RLPHVRKCVVVVLLQGLSLELLDFPPLFWVLDAAHAIWHISTIPVHVLFFSFLEDDSLYLL
KESEDKFKLD

[illegible]

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FIGURE 218

MAPQSLPSSRMAPLGMLLGLLMAACFTFCLSHQNLKEFALTNPEKSSTKETERKETKAEHEEL
DAEVLEVFPHTHEWQALQPGQAVPAGSHVRLNLQTGEREAKLQYEDKFRNNLKGKRLDINTN
TYTSQDLKSALAKFKEGAEMESSKEDKARQAEVKRLFRPIEELKKDFDELNVVIETDMQIMV
RLINKFNSSSSSLEEKIAALFDLEYVHQMDNAQDLLSFGGLQVVINGLNSTEPLVKEYAAF
VLGAAFSSNPKVQVEAIEGGALQKLLVILATEQPLTAKKKVLFALCSLLRHFPYAQRQFLKL
GGLQVLR TLVQEKGTEVLAVRVVTLTYDLVTEKMFEEEEAELTQEMSPEKLQQYRQVHLLPG
LWEQGWCEITAHLLALPEHDAREKVLQTLGVLLTTCRDRYRQDPQLGRTLASLQAEYQVLAS
LELQDGEDEGYFQELLGSVNSLLKELR

FIGURE 219

TTCGGCTTCCGTAGAGGAAGTGGCGCGGACCTTCATTTGGGGTTTCGGTTCCCCCCTTCCC
CTTCCCCGGGGTCTGGGGGTGACATTGCACCGCGCCCTCGTGGGGTTCGCGTTGCCACCCCA
CGCGGACTCCCCAGCTGGCGCGCCCTCCCATTTCCTGTCTCTGGTCAGGCCCCCAGCCCCC
TTCCCACCTGACCAGCCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTGCGGTTTCGGC
CCGGCCTTCGCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGT
CGCAGGGGCATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGG
TCCATGTGACCGACCGGTGAGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCT
GTCTCTGTCTTCTACAGGAGGTGTTCCGCTTTCGCTACTACAAGCTGCTTAAGAAGGCAGA
TGAAGGGTTAGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCT
ATGTTTCTGGTCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCT
GATGCACTTGGGCCAGGTGTGGTTGGGATCCATGGAGACTCACCTATTACTTCCTGACTTC
AGCCTTTCTGACAGCAGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATG
CCTGTGAGAGGAGACGGTACTGGGCTTTGGGCCTGGTGGTTGGGAGTCACCTACTGACATCG
GGACTGACATTCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCATCTATGCAGTCACTGT
TTCCATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCTCCGAAGTATTCAGCGCAGCC
TCTTGTGTAAGGACTGACTACCTGGACTGATCGCCTGACAGATCCCACCTGCCTGTCCACTG
CCCATGACTGAGCCCAGCCCCAGCCGGGTCCATTGCCACATTCTCTGTCTCCTTCTCGTC
GGTCTACCCCACTACCTCCAGGGTTTGTCTTGTCTTTTGTGACCGTTAGTCTCTAAGCTT
TACCAGGAGCAGCCTGGGTTTCCAGCCAGTCAGTGAAGTGGGTTTGAATCTGCACTTATCCC
CACCACCTGGGGACCCCTTGTGTGTCCAGGACTCCCCCTGTGTGCTGCTCTGCTCTCAC
CCTGCCCCAAGACTCACCTCCCTTCCCCCTCTGCAGGCCGACGGCAGGAGGACAGTCGGGTGAT
GGTGTATTCTGCCCTGCGCATCCACCCGAGGACTGAGGGAACCTAGGGGGGACCCCTGGGC
CTGGGGTGGCCTCCTGATGTCTCGCCCTGTATTTCTCCATCTCCAGTTCTGGACAGTGCAG
GTTGCCAAGAAAAGGGACCTAGTTTAGCCATTGCCCTGGAGATGAAATTAATGGAGGCTCAA
GGATAGATGAGCTCTGAGTTTCTCAGTACTCCCTCAAGACTGGACATCTTGGTCTTTTTCTC
AGGCCTGAGGGGGAACCATTTTTTGGTGTGATAAATACCCTAACTGCCTTTTTTTCTTTTTT
GAGGTGGGGGAGGGAGGAGGTATATTGGAACCTTCTAACCTCCTTGGGCTATATTTTCTC
TCCTCGAGTTGCTCCTCATGGCTGGGCTCATTTCCGTCCTTTCTCCTTGGTCCCAGACCTT
GGGGGAAAGGAAGGAAGTGCATGTTTGGGAACCTGGCATTACTGGAATAATGGTTTTAACCT
CCTTAACCACCAGCATCCCTCCTCTCCCCAAGGTGAAGTGGAGGGTGTGTGGTGGAGCTGGC
CACTCCAGAGCTGCAGTGCCACTGGAGGAGTCAGACTACCATGACATCGTAGGGAAGGAGGG
GAGATTTTTTTGTAGTTTTTAATTGGGGTGTGGGAGGGGCGGGGAGGTTTTCTATAAACTGT
ATCATTTTCTGCTGAGGGTGGAGTGTCCCATCCTTTTAATCAAGGTGATTGTGATTTTACT
AATAAAAAAGAATTTGTAAAAA
AA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 220

MGAAVFFGCTFVAFGPALFLITVAGDPLRVIIILVAGAFFWLVSLLLASVVWFILVHVTDR
SDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYVSGLS
FGIISGVFSVINILADALGPGVVGIIHGDSPPYFLTSAFLTAIIILLHTFWGVVFFDACERRR
YWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQRSLCKD

FIGURE 221

AAGCTGGTTTAAGGAAGCAGAGGAGGGTTAGATTCGTTGAGTGAGGACGGAAGATCAACCCA
TTTCCATTCCGCCAGATGGCCTATGTTTCTGGTCTCTCCCTTCGGNATCATCAGTGGTGTNT
TNTCTGTTATCAATATTTTGGCTGATGCANTTGGGCCAGGTGTGGTTGGGATCCATGGAGAC
TCACCCTATTANTTCCTGANTTCAGCCTTTNTGACAGCAGCCATTATCCTGCTC

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FIGURE 222

GACCGACCGTTCAGATGCCCGGTTCCAGTACGGCTTCCTGATTTTTGGTGCTGCTGTNTCTG
TCCTTCTACAGGAGGTGTTCCGCTTTGCCTANTACAAGCTGCTTAAGAAGGCAGATGAGGGG
TTAGCATNGCTGAGTGAGGACGGAAGATCACCCATTTCCATCCGCCAGATGGCCTATGTTTN
TGGTNTTTCCTTCGGTATCATCAGTGGTGTTTTNTCTGTTATCAATATTTTGGNTGATGCAN
TTGGGCCAGGTGTGGTTGGGATCCATGGAGANTCACCTATTAATTCCTGAATTCAGCCTTT
NTGACAGCAGCCATTATCCTGNTCCATACCTTTTGGGGAGTTGTGTTTTTTGATGCCTGTGA
GAGGAG

FIGURE 223

NGTTGGAGAAGTGGCGCGGACNTTCATTTGGGGTTTCGGTTTCCCCCTTTCCCTTTCCCCG
GGGTCTGGGGTGACATTGCACGGGCCCCCTCGTGGGGTCGCGTTGCCACCCACGCGGACTCC
CCAGNTGGNGCGCCCTTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCTTTCCCACNTG
ACCAGCCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTGCGGTTTCGGCCCGGCCTTCG
CGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTCGCAGGGGCA
TTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGGTCCATGTGAC
CGACCGGTCAGATGCCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTCC
TTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGATGAGGGGTTA
GCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTGG
TCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTTG
GGCCAGGTGTGGTTGGGATCCATGGAGACTCACCC

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FIGURE 224

GTAAAAGAAAGTGGCCGGACCTTCATTGGGGTTTCGGTTCCCCCCTTCCCNNTTCCCCGGGG
TCTGGGGGTGACATTGCACCGCGCCCNCTCGTGGGGTCGCGTTGCCACCCACGCGGACTCCC
CAGNTGGCGCGCCCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCCTTCCCACCTGA
CCAGCCATGGGGGCTGCGGTGTTTTTCGGGCTGCACTTTCGTGCGGTTGGGGCCCGGCCTTC
GCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTTCGAGGGGC
ATTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGGTCCATGTGA
CCGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTC
CTTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGATGAGGGGTT
AGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTG
GTCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTT
GGGCCAGGTGTGGTTGGGATCCATGGAGAC

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FIGURE 225

GCCCCAGGGAGCAGTGGGTGGTTATAACTCAGGCCCGGTGCCAGAGCCCAGGAGGAGGCAG
TGGCCAGGAAGGCACAGGCCTGAGAAGTCTGCGGCTGAGCTGGGAGCAAATCCCCACCCCC
TACCTGGGGGACAGGGCAAGTGAGACCTGGTGAGGGTGGCTCAGCAGGCAGGGAAGGAGAGG
TGTCTGTGCGTCCTGCACCCACATCTTTCTCTGTCCCCTCCTTGCCCTGTCTGGAGGCTGCT
AGACTCCTATCTTCTGAATTCTATAGTGCCTGGGTCTCAGCGCAGTGCCGATGGTGGCCCGT
CCTTGTGGTTTCCTCTCTACCTGGGGAAATAAGGTGCAGCGGCCCATGGCTACAGCAAGACCCC
CCTGGATGTGGGTGCTCTGTGCTCTGATCACAGCCTTGCTTCTGGGGGTACAGAGCATGTT
CTCGCCAAACAATGATGTTTCCTGTGACCACCCCTCTAACACCGTGCCCTCTGGGAGCAACCA
GGACCTGGGAGCTGGGGCCGGGGAAGACGCCCGGTGCGATGACAGCAGCAGCCGCATCATCA
ATGGATCCGACTGCGATATGCACACCCAGCCGTGGCAGGCCGCGCTGTTGCTAAGGCCCAAC
CAGCTCTACTGCGGGGCGGTGTTGGTGATCCACAGTGGCTGCTCACGGCCGCCCCTGTCAG
GAAGAAAGTTTTTCAGAGTCCGTCTCGGCCACTACTCCCTGTACCAGTTTTATGAATCTGGGC
AGCAGATGTTCCAGGGGGTCAAATCCATCCCCACCCCTGGCTACTCCCACCCCTGGCCACTCT
AACGACCTCATGCTCATCAAACCTGAACAGAAGAATTCGTCCCACTAAAGATGTCAGACCCAT
CAACGTCTCCTCTCATTGTCCCTCTGCTGGGACAAAGTGCTTGGTGTCTGGCTGGGGGACAA
CCAAGAGCCCCCAAGTGCACTTCCCTAAGGTCCTCCAGTGCTTGAATATCAGCGTGCTAAGT
CAGAAAAGGTGCGAGGATGCTTACCCGAGACAGATAGATGACACCATGTTCTGCGCCGGTGA
CAAAGCAGGTAGAGACTCCTGCCAGGGTGATTCTGGGGGGCCTGTGGTCTGCAATGGCTCCC
TGCAGGGACTCGTGTCTTGGGGAGATTACCCTTGTGCCCCGGCCCAACAGACCGGGTGTCTAC
ACGAACCTCTGCAAGTTCACCAAGTGATCCAGGAAACCATCCAGGCCAACTCCTGAGTCAT
CCCAGGACTCAGCACACCGGCATCCCCACCTGCTGCAGGGACAGCCCTGACACTCCTTTTCAG
ACCCTCATTCCTTCCCAGAGATGTTGAGAATGTTTCATCTCTCCAGCCCCTGACCCCATGTCT
CCTGGACTCAGGGTCTGCTTCCCCACATTGGGCTGACCGTGTCTCTCTAGTTGAACCCTGG
GAACAATTTCCAAAACCTGTCCAGGGCGGGGGTTGCGTCTCAATCTCCCTGGGGCACTTTCAT
CCTCAAGCTCAGGGCCCATCCCTTCTCTGCAGCTCTGACCCAAATTTAGTCCCAGAAATAAA
CTGAGAAGTGAAAAA

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FIGURE 226

MATARPPWMVLCALITALLGVTEHVLANNVSCDHPSNTVPSGSNQDLGAGAGEDARSDD
SSSRIINGSDCDMHTQPWQAALLLRPNQLYCGAVLVHPQWLLTAAHCRKKVFRVRLGHYSLS
PVYESGQQMFQGVKSI PHPGYSHPGHSNDLMLIKLNRRIRPTKDVRPINVSSHCP SAGTKCL
VSGWGTTKSPQVHF PKVLQCLNISVLSQKRCEDAYPRQIDDTMFCAGDKAGR DSCQGD SGGP
VVCNGSLQGLVSWGDYPCARPNRPGVYTNLCKFTKWIQETIQANS

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FIGURE 227

ATGGTCAACGACCGGTGGAAGACCATGGGCGGCGCTGCCCAACTTGAGGACCGGCCGCGCGA
CAAGCCGACGCGCCGAGCTGCGGCTACGTGCTGTGCACCGTGCTGCTGGCCCTGGCTGTGC
TGCTGGCTGTAGCTGTACCCGGTGCCGTGCTCTTCTCTGAACCACGCCCACGCGCCGGGCACG
GCGCCCCACCTGTCTGTAGCTGTGAGCTGGGGCTGCCAGCGCCAACAGCGCCCTGGTCACTGTGGA
AAGGGCGGACAGCTCGCACCTCAGCATCCTCATTGACCCGCGCTGCCCCGACCTCACCAGCA
GCTTCGCACGCCTGGAGAGCGCCAGGCCCTCGGTGCTGCAGGCGCTGACAGAGCACCAGGCC
CAGCCACGGCTGGTGGGCGACCAGGAGCAGGAGCTGCTGGACACGCTGGCCGACCAGCTGCC
CCGGCTGCTGGCCCGAGCCTCAGAGCTGCAGACGGAGTGATGGGGCTGCGGAAGGGGCATG
GCACGCTGGGCCAGGGCCTCAGCGCCCTGCAGAGTGAGCAGGGCCGCTCATCCAGCTTCTC
TCTGAGAGCCAGGGCCACATGGCTCACCTGGTGAACCTCCGTACAGCGACATCCTGGATGCCCT
GCAGAGGGACCGGGGGCTGGGCCGGCCCCGCAACAAGGCCGACCTTCAGAGAGCGCCTGCCC
GGGGAACCCGCCCCGGGGCTGTGCCACTGGCTCCCGCCCCGAGACTGTCTGGACGTCCTC
CTAAGCGGACAGCAGGACGATGGCGTCTACTGTCTTTTCCACCCACTACCCGGCCGGCTT
CCAGGTGTACTGTGACATGCGCACGGACGGCGGGCTGGACGGTGTTCAGCGCCGGGAGG
ACGGCTCCGTGAACCTTCTTCCGGGGCTGGGACGCGTACCGAGACGGCTTTGGCAGGCTCACC
GGGGAGCACTGGCTAGGGCTCAAGAGGATCCACGCCCTGACCACACAGGCTGCCTACGAGCT
GCACGTGGACCTGGAGGACTTTGAGAATGGCACGGCCTATGCCCGCTACGGGAGCTTCGGCG
TGGGCTTGTTCTCCGTGGACCTGAGGAAGACGGGTACCCGCTCACCGTGGCTGACTATTCC
GGCACTGCAGGCGACTCCCTCCTGAAGCACAGCGGCATGAGGTTTACCACCAAGGACCGTGA
CAGCGACCATTCAGAGAACAACCTGTGCCGCTTCTACCGCGGTGCCTGGTGGTACCGCAACT
GCCACACGTCCAACCTCAATGGGCAGTACCTGCGCGGTGCGCACGCCTCCTATGCCGACGGC
GTGGAGTGGTCTCCTGGACCGGCTGGCAGTACTCACTCAAGTTCTCTGAGATGAAGATCCG
GCCGGTCCGGGAGGACCGCTAGACTGGTGACCTTGTCTTGGCCCTGCTGGTCCCTGTGCG
CCCATCCCCGACCCACCTCACTCTTTCGTGAATGTTCTCCACCCACCTGTGCCTGGCGGAC
CCACTCTCCAGTAGGGAGGGGCGGGCCATCCCTGACACGAAGCTCCCTGGGCGGTGAAGT
CACACATCGCCTTCTCGCCGTCCCCACCCCTCCATTTGGCAGCTCACTGATCTCTTGCCCTC
TGCTGATGGGGCTGGCAAACCTTGACGACCCCAACTCCTGCCTGCCCCACTGTGACTCCGG
TGCTGTTTGGCGTCCCCTGGCCAGGATGGTGGAGTCTGCCCCAGGCACCTCTGCCCTGCC
GGCAAATACCCGGCATTATGGGGACAGAGAGAGGGGGCAGACAGCACCCCTGAGGAGCTC
CTAGCAGATCGTGGGGAATGTCAGGTCTCTCTGAGGTGAGGTCTGAGGCCAGTATCCTCCAG
CCCTCCCAATGCCAACCCCAACCCGTTTCCCTGGTGCCAGAGAACCACCTCTCCCCCAA
GGGCCTCAGCCTGGCTGTGGGCTGGGTGGCCCATCCTACCAGGCCCTGAGGTGAGGATGGG
GAGCTGCTGCCTTTGGGGACCCACGCTCCAAGGCTGAGACCAGTTCCCTGGAGGCCACCCAC
CCTGTGCCCCGGCAGGCCTGGGGTCTGCAGTCTCTTACCTGCTGTGCCACCTGCTCTCTG
TCTCAAATGAGGCCCAACCCATCCCCACCCAGCTCCCGCCGTCCTCCTACCTGGGGCAGC
CGGGGCTGCCATCCCATTCTCCTGCCTCTGGAAGGTGGGTGGGGCCCTGCACCGTGGGGCT
GGACTGCGCTAATGGGAAGCTCTTGGTTTTCTGGGCTGGGGCCTAGGCAGGGCTGGGATGAG
GCTTGTAACAACCCCAACCAATTTCCAGGGACTCCAGGGTCTGAGGCCTCCAGGAGG
GCCTTGGGGGTGATGACCCCTTCCCTGAGGTGGCTGTCTCCATGAGGAGGCCAACCTTGCC
ATTGACCGTGGCCACCTGGACCCAGGCCAGGCCCGGCCGAGTGGTCAAGGGACAGGGA
CCACCTCACCGGGCAAATGGGGTGGGGGGGACTGGGGCACCAGACCAGGCACCACCTGGACA
CTTTCTTGTTGAATCCTCCCAACCCAGCACGCTGTATCCCCACTCCTTGTTGTGCACACA
TGCAGAGGTGAGACCCGCAGGCTCCCAGGACCAAGGCCAGGGCTGGAGCCGGG
TCCTCAGCTGTCTGCTCAGCAGCCCTGGACCCGCGTGCGTTACGTGAGGCCAGATGCAGGG
CGGCTTTTCCAAGGCCTCCTGATGGGGGCTCCGAAAGGGCTGGAGTCAGCCTTGGGGAGCT
GCCTAGCAGCCTCTCCTCGGGCAGGAGGGGAGGTGGCTTCTCCAAAGGACACCCGATGGCA
GGTGCTAGGGGTGTGGGGTTCGTTCTCCCTTCCCTCCCACTGAAGTTTGTGCTTAAAA
AACAATAAATTTGACTTGGCACCCTGGGGGTTGGTGGGAGAGGCCGTGTGACCTGGCTCTC
TGTCCAGTGCCACCAGGTATCCACATGCGCAG

FIGURE 228

MVNDRWKTMGGAAQLEDPRDKPQRPSCGYVLCTVLLALAVLLAVAVTGAVLFLNHAHAPGT
APPPVVSTGAASANSALVTVERADSSHLSILIDPRCPDLTDSFARLESAQASVLQALTEHQA
QPRLVGDQEQELLDTLADQLPRLRARASELQTECMGLRKGHGTLGQGLSALQSEQGRLIQLL
SESQGHMAHLVNSVSDILDALQRDRGLGRPRNKADLQRAPARGTRPRGCATGSRPRDCLDVL
LSGQQDDGVYSVFPPTHYPAGFQVYCDMRTDGGGWTVFQRRDGSVNFFRGWDAYRDGFGRLT
GEHWLGLKRIHALTTQAAYELHVDLED FENG TAYARYGSFGVGLFSVDPEEDGYPLTVADYS
GTAGDSLLKHSGMRFTTKDRDSDHSENNCAAFYRGAWWYRNCHTSNLNGQYLRGAHAS YADG
VEWSSWTGWQYSLKFSEMKIRPVREDR

FIGURE 229

GCAGTCAGAGACTTCCCCTGCCCCCTCGCTGGGAAAGAACATTAGGAATGCCTTTTAGTGCCT
TGCTTCCTGAACTAGCTCACAGTAGCCCGGCGGCCAGGGCAATCCGACCACATTTCACTCT
CACCGCTGTAGGAATCCAGATGAGGCCAAGTACAGCAGCACGAGGGACATGCTGGATGATG
ATGGGGACACCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACCTCGGCATCCAGAGCCC
CGGCGCACAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGACCCTGCTGAC
TTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTTCAGTACTACC
AGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGATTAGGAAATACGTCC
CAAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTCTGCAGCATGTGGC
TGAAAACTCTGTGCTGAGCTGTATACAAAGCTGGAGCACACAGGTGCAGCCCTTGTACAG
AACAAATGGAAATGGCATGGAGACAATTGCTACCAGTTCTATAAAGACAGCAAAAAGTTGGGAG
GACTGTAAATATTTCTGCCTTAGTGAAAACCTCTACCATGCTGAAGATAAAACAAACAAGAAGA
CCTGGAATTTGCCGCGTCTCAGAGCTACTCTGAGTTTTTCTACTCTTATTGGACAGGGCTTT
TGCGCCCTGACAGTGGCAAGGCCTGGCTGTGGATGGATGGAACCCCTTTCACTTCTGAACTG
TTCCATATTATAATAGATGTCACCAGCCCCAAGAAGCAGAGACTGTGTGGCCATCCTCAATGG
GATGATCTTCTCAAAGGACTGCAAAGAATTGAAGCGTTGTGTCTGTGAGAGAAGGGCAGGAA
TGGTGAAGCCAGAGAGCCTCCATGTCCCCCTGAAACATTAGGCGAAGGTGACTGATTCGCC
CTCTGCAACTACAAATAGCAGAGTGAGCCAGGCGGTGCCAAAGCAAGGGCTAGTTGAGACAT
TGGGAAATGGAACATAATCAGGAAAGACTATCTCTCTGACTAGTACAAAATGGGTTCTCGTG
TTTCCTGTTTACAGGATCACCAGCATTTCTGAGCTTGGGTTTATGCACGTATTTAACAGTCACA
AGAAGTCTTATTTACATGCCACCAACCAACCTCAGAAACCCATAATGTCATCTGCCTTCTTG
GCTTAGAGATAACTTTTAGCTCTCTTTCTTCTCAATGTCTAATATCACCTCCCTGTTTTTCAT
GTCTTCCTTACACTTGGTGGAAATAAGAACTTTTTGAAGTAGAGGAAATACATTGAGGTAAC
ATCCTTTTCTCTGACAGTCAAGTAGTCCATCAGAAATTGGCAGTCACTTCCCAGATTGTACC
AGCAAATACACAAGGAATTCTTTTTGTTTGTTCAGTTCATACTAGTCCCTTCCCAATCCAT
CAGTAAAGACCCCATCTGCCTTGTCCATGCCGTTTCCCAACAGGGATGTCACTTGATATGAG
AATCTCAAATCTCAATGCCTTATAAGCATTCTTCTGTGTCCATTAAGACTCTGATAATTG
TCTCCCCTCCATAGGAATTTCTCCCAGGAAAGAAATATATCCCCATCTCCGTTTCATATCAG
AACTACCGTCCCCGATATTCCCTTCAGAGAGATTAAAGACCAGAAAAAAGTGAGCCTCTTCA
TCTGCACCTGTAATAGTTTCAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTTCA
GTACTGAAGATTTAATAATAATAAATGTAAATACTGTGAAAAA

FIGURE 230

MQAKYSSTRDMLDDDGDTTMSLHSQASATTRHPEPRRTEHRAPSSTWRPVALTLLTLCLVLL
IGLAALGLLFFQYYQLSNTGQDTISQMEERLGNTSQELQSLQVQNIKLAGSLQHVAEKLCRE
LYNKAGAHRCSPCTEQWKWHGDNCYQFYKDSKSWEDCKYFCLSENSTMLKINKQEDLEFAAS
QSYSEFFYSYWTGLLRPDSGKAWLWMDGTPFTSELFHIIIDVTSPRSRDCVAILNGMIFSKD
CKELKRCVCERRAGMVKPESLHVPPETLGEGD

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FIGURE 231

AATTTTCACCGCTGTAGGAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGNTGG
ATGATGATGGGACACCACCATGAGCCTGCATTNTCAAGCTTTTGCCACAATTCGGCATCCAG
AGCCCCGGCGCACAGAGCACAGGGNTCCTTTTTCAACGTGGCGACCAGTGGCCCTGACCCTG
CTGACTTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTCAGTA
CTACCAGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGATTAGGAAATA
CGTCCCAAGAGTTGCAATTTNTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTNTGCAGCAT
GTGGCTGAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGGAACTTTGAAGGAGGGCAA
AGTNTCCTCATNTACTATACACACACCACTTCCC

FIGURE 232

GCCGAGCGCAAGAACCCCTGCGCAGAGCCAGAGCAGCTGCTGGAGGGGAATCGAGGCGCGGCT
 CGGGGATTTCGGCTCGGGCCGCTGGCTCTGCTCTGCGGGGAGGGAGCGGGCCCCGCGCGGG
 CCGAGCCCTCCGGATCCGCCCCCTCCCGGTCCCGCCCCCTCGGAGACTCCTCTGGCTGCT
 CTGGGGGTTTCGCGGGGGCCGGGGACCCGCGGTCCGGGCGCCATGCGGGCATCGCTGCTGCTG
 TCGGTGCTGCGGCCCCGAGGGCCCGTGGCCGTGGGCATCTCCCTGGGCTTACCCTGAGCCT
 GCTCAGCGTCACCTGGGTGGAGGAGCCGTGCGGCCAGGCCCGCCCCAACCTGGAGACTCTG
 AGCTGCCCGCCGCGCGGCAACACCAACGCGGCGCGCCGGCCCCAACTCGGTGCAGCCCGGAGCG
 GAGCGCGAGAAGCCCGGGGCGGGCGAAGGCGCCGGGAGAATTGGGAGCCGCGCGTCTTGCC
 CTACCACCTTGACAGCCCGGCCAGGCCGCCAAAAAGGCCGTAGGACCCGCTACATCAGCA
 CGGAGCTGGGCATCAGGCAGAGGCTGCTGGTGGCGGTGCTGACCTCTCAGACCACGTGCC
 ACGCTGGGCGTGGCCGTGAACCGCACGCTGGGGCACCGGCTGGAGCGTGTGGTGTTCCTGAC
 GGGCGCACGGGGCCGCGGGGCCCCACCTGGCATGGCAGTGGTGACGCTGGGCGAGGAGCGAC
 CCATTGGACACCTGCACCTGGCGCTGCGCCACCTGCTGGAGCAGCACGGCGACGACTTTGAC
 TGGTTCTTCTGGTGCTGACACCCTACACCGAGGCGCACGGCCTGGCACGCCTAACTGG
 CCACCTCAGCCTGGCCTCCGCGGCCACCTGTACCTGGGCGGGCCCCAGGACTTCATCGCG
 GAGAGCCCCACCCCGGCCGCTACTGCCACGGAGGCTTTGGGGTGCTGCTGTGCGCATGCTG
 CTGCAACAACTGCGCCCCACCTGGAAGGCTGCCGCAACGACATCGTCAGTGCGCGCCCTGA
 CGAGTGGCTGGGTGCTGCAATTCTCGATGCCACCGGGGTGGGCTGCACTGGTGACCACGAGG
 GGGTGCACTATAGCCATCTGGAGCTGAGCCCTGGGGAGCCAGTGACAGGAGGGGGACCCTCAT
 TTCCGAAGTGCCCTGACAGCCCACCCTGTGCGTGACCCTGTGCACATGTACCAGCTGCACAA
 AGCTTTTCGCCCCGAGCTGAACTGGAACGCGACGTACCAGGAGATCCAGGAGTTACAGTGGGAGA
 TCCAGAATACCAGCCATCTGGCCGTTGATGGGGACCGGGCAGCTGCTTGGCCCGTGGGTATT
 CCAGCACCATCCCGCCCGGCCTCCCGCTTTGAGGTGCTGCGCTGGGACTACTTCACGGAGCA
 GCACGCTTTCTCCTGCGCCGATGGCTCACCCCGCTGCCCACTGCGTGGGGCTGACCGGGCTG
 ATGTGGCCGATGTTCTGGGGACAGCTCTAGAGGAGCTGAACCGCCGCTACCACCCGGCCTTG
 CGGCTCCAGAAGCAGCAGCTGGTGAATGGCTACCGACGCTTTGATCCGGCCCCGGGGTATGGA
 ATACACGCTGGACTTGACGCTGGAGGCACTGACCCCCCAGGGAGGCCGCGGGCCCCCTCACTC
 GCCGAGTGACGCTGCTCCGGCCGCTGAGCCGCGTGAGATCTTGCCCTGTGCCCTATGTCACT
 GAGGCCTCACGTCTCACTGTGCTGCTGCCTCTAGCTGCGGCTGAGCGTGACCTGGCCCCCTGG
 CTTCTTGAGAGCCTTTGCCACTGCAGCACTGGAGCCTGGTGATGCTGCGGCAGCCCTGACCC
 TGCTGCTACTGTATGAGCCGCGCCAGGCCAGCGCGTGGCCCATGCAGATGTCTTCGCACCT
 GTCAAGGCCCACGTGGCAGAGCTGGAGCGGCGTTTCCCGGTGCCCGGGTGCCATGGCTCAG
 TGTGCAGACAGCCGCACCCTCACCACTGCGCCTCATGGATCTACTCTCCAAGAAGCACCCGC
 TGGACACACTGTTCTGCTGGCCGGGCCAGACACGGTGCTCACGCCTGACTTCTGAACCGC
 TGCCGATGCATGCCATCTCCGGCTGGCAGGCCTTCTTCCCATGCATTTCCAAGCCTTCCA
 CCCAGGTGTGGCCCCACCACAAGGGCCTGGGCCCCCAGAGCTGGGCCGTGACACTGGCCGCT
 TTGATCGCCAGGCAGCCAGAGGCGCTTCTACAACCTCCGACTACGTGGCAGCCCGTGGG
 CGCCTGGCCGCGAGCCTCAGAACAAGAGGAGGAGCTGCTGGAGAGCCTGGATGTGTACGAGCT
 GTTCTCTCACTTCTCCAGTCTGCATGTGCTGCGGGCGGTGGAGCCGCGCTGCTGCACGCT
 ACCGGGCCCAGACGTGCAGCGCGAGGCTCAGTGAGGACCTGTACCACCGCTGCCCTCCAGAGC
 GTGCTTGAGGGCCTCGGCTCCCGAACCAGCTGGCCATGCTACTTTTGAACAGGAGCAGGG
 CAACAGCACCTGAACCCCCACCTGTCCCCGTGGGCCGTGGCATGGCCACACCCACCCCACTT
 CTCCCCCAAACACAGAGCCACCTGCCAGCCTCGCTGGGCAGGGCTGGCCGTAGCCAGACCCC
 AAGCTGGCCCCACTGGTCCCCTCTCTGGCTCTGTGGGTCCCTGGGCTCTGGACAAGCACTGGG
 GGACGTGCCCCCAGAGCCACCCACTTCTCATCCCAAACCCAGTTTCCCTGCCCCCTGACGCT
 GCTGATTTCGGGCTGTGGCCCTCCACGTATTTATGCAGTACAGTCTGCCTGACGCGCAGCCCTGC
 CTCTGGGCCCCTGGGGGCTGGGCTGTAGAAGAGTTGTTGGGGAAGGAGGGAGCTGAGGAGGGG
 GCATCTCCCAACTTCTCCCTTTTGGACCCTGCCGAAGCTCCCTGCCTTTAATAAACTGGCCA
 AGTGTGGAAAAA

FIGURE 233

MRASLLLSVLRPAGPVAVGISLGFTLSLLSVTWVEEPCGPGPPQPGDSELPPRGNTNAARRP
NSVQPGAEREKPGAGEGAGENWEPRVLPYHPAQPGQAACKAVRTRYISTELGIRQRLLVAVL
TSQTTLPTLGAVNRTLGHRLERVVFLTGARGRRAPPGMAVVTLGEERPIGHLHLALRHLLLE
QHGDDEFDWFFLVPDTTYTEAHGLARLTGHLSLASAAHLYLGRPQDFIGGEPTPGRYCHGGFG
VLLSRMLLQQLRPHLEGCRNDIVSARPDEWLGRCILDATGVGCTGDHEGVHYSHLELSPGEP
VQEGDPHFERSALTAHPVRDPVHMYQLHKAFARAELETTYQEIQELQWEIQNTSHLAVDGDRA
AAWPVGIPAPSRPASRFEVLRWDYFTEQHAFSCADGSPRCPLRGADRADVADVLTALAEELN
RRYHPALRLQKQQLVNGYRRFDPARGMEYTLDLQLEALTPQGRRPLTRRVQLLRPLSRVEI
LPVPYVTEASRLTVLLPLAAAERDLAPGFLEAFATAALEPGDAAAALTLLLLYEPRQAQRVA
HADVFAPVKAHVAELERRFPGARVPWLSVQTAAPSPLRLMDLLSKKHPLDTLFLLAGPDTVL
TPDFLNRCRMHAISGWQAFFPMHFQAFHPGVAPPQGPPELGRDTGRFDRQAASEACFYNS
DYVAARGRLAAASEQEEELLESLDVYELFLHFSSLHVLRAVEPALLQRYRAQTCSARLSEDL
YHRCLQSVLEGLGSRTQLAMLLFEQEQGNST

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FIGURE 234

GCTCTGGCCGGCCCCGGCGATTGGTCACCGCCCGCTAGGGGACAGCCCTGGCCTCCTCTGAT
TGGCAAGCGCTGGCCACCTCCCCACACCCCTTGCGAACGCTCCCCTAGTGGAGAAAAGGAGT
AGCTATTAGCCAATTCGGCAGGGCCCGCTTTTGTAGAAGCTTGATTTCTTTGAAGATGAAAG
ACTAGCGGAAGCTCTGCCTCTTTCCCCAGTGGGCGAGGGAACTCGGGGCGATTGGCTGGGAA
CTGTATCCACCCAAATGTCACCGATTTCTTCTTATGCAGGAAATGAGCAGACCCATCAATAA
GAAATTTCTCAGCCTGGCCGAAAATGGTTGGCCCCACGAAGCCACGACAACTGGAGGCAAAG
AGGGTTGCTCAACGCCCCGCCTCATTGGAAAACCAAATCAGATCTGGGACCTATATAGCGTG
GCGGAGGCGGGGCGATGATTGTCGCGCTCGCACCCACTGCAGCTGCGCACAGTCGCATTTCT
TTCCCCGCCCCTGAGACCCTGCAGCACCATCTGTCAATGGCGGCTGGGCTGTTTGGTTTGAGC
GCTCGCCGTCTTTTGGCGGCAGCGGCGACGCGAGGGCTCCCGGCCGCCCCTCGCTCCGCTGGGA
ATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCTGTGGCGGGAAAGCGGCCCCCAGAAC
CGACCACACCGTGGCAAGAGGACCCAGAACCCGAGGACGAAAACCTGTATGAGAAGAACCCA
GACTCCCATGGTTATGACAAGGACCCGTTTTTGGACGTCTGGAACATGCGACTTGTCTTCTT
CTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACCTTTGTGGCCTATCTGCCTGACTACA
GGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCTTGTGAAATACCGAGAGGCCAATGGC
CTTCCCATCATGGAATCCAACCTGCTTCGACCCAGCAAGATCCAGCTGCCAGAGGATGAGTG
ACCAGTTGCTAAGTGGGGCTCAAGAAGCACCGCCTTCCCCACCCCCTGCCTGCCATTCTGAC
CTCTTCTCAGAGCACCTAATTAAAGGGGCTGAAAGTCTGAA

FIGURE 235

MAAGLFGLSARRLLAAAATRGLPAARVRWESSFSRTVVAPSAVAGKRPPEPTTPWQEDPEPE
DENLYEKNPDSHGDKDPVLDVWNMRLVFFFGVSIILVLGSTFVAYLPDYRMKEWSRREAER
LVKYREANGLPIMESNCFDPSKIQLPED

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FIGURE 236

GGCGGCTGGGCTGTTTGGTTTGAGCGCTCGCCGTCTTTTGGCGGCAGCGGCGACGCGAGGGC
TCCCGGCCGCCCCGCTCCGCTGGGAATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCT
GTGGCGGGAAAGCGGCCCCCAGAACCGACCACACCGTGGCAAGAGGACCCAGAACCCGAGGA
CGAAAACCTTGATGAGAAGAACCAGACTCCCATGGTTATGACAAGGACCCGTTTGGACG
TCTGGAACATGCGACTTGTCTTCTTCTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACC
TTTGTGGCCTATCTGCCTGACTACAGGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCT
TGTGAAATACCGAGAGGCCAATGGCCTTCCCATCATGGAATCCAAGTCTTCGACCCAGCA
AGATCCAG

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FIGURE 237

GCGGCGGCTATGCCGCTTGCTCTGCTCGTCCTGTTGCTCCTGGGGCCCGGCGGCTGGTGCCT
TGCAGAACCCCCACGCGACAGCCTGCGGGAGGAACTTGTCAACCCCGCTGCCTTCCGGGG
ACGTAGCCGCCACATTCCAGTTCCGCACGCGCTGGGATTTCGGAGCTTCAGCGGGAAGGAGTG
TCCCATTAACAGGCTCTTTCCCAAAGCCCTGGGGCAGCTGATCTCCAAGTATTCTCTACGGGA
GCTGCACCTGTCAATTCACACAAGGCTTTTGGAGGACCCGATACTGGGGGCCACCCTTCTGCG
AGGCCCCATCAGGTGCAGAGCTGTGGGTCTGGTTCCAAGACACTGTCACTGATGTGGATAAA
TCTTGGAAGGAGCTCAGTAATGTCTCTCAGGGATCTTCTGCGCCTCTCTCAACTTCATCGA
CTCCACCAACACAGTCACTCCCACTGCCTCCTTCAAACCCCTGGGTCTGGCCAATGACACTG
ACCACTACTTTCTGCGCTATGCTGTGCTGCCGCGGGAGGTGGTCTGCACCGAAAACCTCACC
CCCTGGAAGAAGCTCTTGCCCTGTAGTTCCAAGGCAGGCCTCTCTGTGCTGCTGAAGGCAGA
TCGCTTGTTCCACACCAGCTACCACTCCCAAGCAGTGCATATCCGCCCTGTTTGCAGAAATG
CACGCTGTACTAGCATCTCCTGGGAGCTGAGGCAGACCCTGTCAGTTGTATTGATGCCTTC
ATCACGGGGCAGGGAAAGAAAGACTGGTCCCTCTTCCGGATGTTCTCCCGAACCCCTCACGGA
GCCCTGCCCCCTGGCTTCAGAGAGCCGAGTCTATGTGGACATCACCACCTACAACCAGGACA
ACGAGACATTAGAGGTGCACCCACCCCGACCACTACATATCAGGACGTCATCCTAGGCACT
CGGAAGACCTATGCCATCTATGACTTGCTTGACACCGCCATGATCAACAACCTCTCGAAACCT
CAACATCCAGCTCAAGTGGAAGAGACCCCAAGAGAATGAGGCCCGCCAGTGCCCTTCTCTGC
ATGCCCAGCGGTACGTGAGTGGCTATGGGCTGCAGAAGGGGGAGCTGAGCACACTGCTGTAC
AACACCCACCCATACCGGGCCTTCCCGGTGCTGCTGCTGGACACCGTACCCTGGTATCTGCG
GCTGTATGTGCACACCCTCACCATCACCTCCAAGGGCAAGGAGAACAAACCAAGTTACATCC
ACTACCAGCCTGCCCAGGACCGGCTGCAACCCACCTCCTGGAGATGCTGATTTCAGCTGCCG
GCCAACTCAGTCACCAAGGTTTCCATCCAGTTTGAGCGGGCGCTGCTGAAGTGGACCGAGTA
CACGCCAGATCCTAACCATGGCTTCTATGTGAGCCCATCTGTCTCAGCGCCCTTGTGCCCA
GCATGGTAGCAGCCAAGCCAGTGGACTGGGAAGAGAGTCCCTCTTCAACAGCCTGTTCCCA
GTCTCTGATGGCTCTAACTACTTTGTGCGGCTCTACACGGAGCCGCTGCTGGTGAACCTGCC
GACACCGGACTTCAGCATGCCCTACAACGTGATCTGCCTCACGTGCACTGTGGTGGCCGTGT
GCTACGGCTCCTTCTACAATCTCCTCACCCGAACCTTCCACATCGAGGAGCCCCGCACAGGT
GGCCTGGCCAAGCGGCTGGCCAACCTTATCCGGCGCGCCGAGGTGTCCCCCACTCTTGATT
CTTGCCCTTTCCAGCAGCTGCAGCTGCCGTTTCTCTCTGGGGAGGGGAGCCCAAGGGCTGTT
TCTGCCACTTGCTCTCCTCAGAGTTGGCTTTTGAACCAAAGTGCCCTGGACCAGGTGAGGGC
CTACAGCTGTGTTGTCCAGTACAGGAGCCACGAGCCAAATGTGGCATTTGAATTTGAATTAA
CTTAGAAATTCAATTCCTCACCTGTAGTGGCCACCTCTATATTGAGGTGCTCAATAAGCAAA
AGTGGTCGGTGGCTGCTGTATTGGACAGCACAGAAAAAGATTTCCATCACCAAGAAAGGTC
GGCTGGCAGCACTGGCCAAGGTGATGGGGTGTGCTACACAGTGTATGTCACTGTGTAGTGGA
TGGAGTTTACTGTTTGTGGAATAAAAAACGGCTGTTTCCGTGGAAAAAAAAAAAAA

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FIGURE 238

MPLALLVLLLLGPGGWCLAEP PRDSLREELVITPLPSGDVAATFQFRTRWDSELQREGVSHY
RLFPKALGQLISKYSLRELHLSFTQGFWRTYWGPPFLQAPSGAELWVWFQDTVTDVDKSWK
ELSNVLSGIFCASLNFIDSTNTVTPTASF KPLGLANDTDHYFLRYAVLPREVVCTENLTPWK
KLLPCSSKAGLSVLLKADRLFHTSYHSQAVHIRPVCRNARCTSI SWELRQTL SVVFDAFITG
QGKKDWSLFRMFSRTLTEPCPLASESRVYVDITTYNQDNETLEVHPPPTTTYQDVILGTRKT
YAIYDLLDTAMINNSRNLNIQLKWKRPPENEAPPVPFLHAQRYVSGYGLQKGELSTLLYNTH
PYRAFPVLLLDTPWPYLRLYVHTLTITSKGKENKPSYIHYQPAQDR LQPHLLEMLIQLPANS
VTKVSIQFERALLKWTEYTPDPNHGFYVSPSVLSALVPSMVAAPVDWEESPLFNSLFPVSD
GSNYFVRLYTEPLL VNLPTPDFSMPYNVICLTCTVAVCYGSFYNLLTRTFHIEEPRTGGLA
KRLANLIRRARGVPPL

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FIGURE 239

CAACATGGGGTCCAGCAGCTTCTTGGTCCTCATGGTGTCTCTCGTTCTTGTGACCCTGGTGG
CTGTGGAAGGAGTTAAAGAGGGTATAGAGAAAGCAGGGGTTTGCCCAGCTGACAACGTACGC
TGCTTCAAGTCCGATCCTCCCCAGTGTACACAGACCAGGACTGTCTGGGGGAAAGGAAGTG
TTGTTACCTGCACTGTGGCTTCAAGTGTGTGATTCTGTGAAGGAACTGGAAGAAGGAGGAA
ACAAGGATGAAGATGTGTCAAGGCCATACCCTGAGCCAGGATGGGAGGCCAAGTGTCCAGGC
TCCTCCTCTACCAGGTGTCCTCAGAAATGATGCTGGGTCTTTCTACCTCTGGGGGTCACTC
TCACTTGGCACCTGCCCCCTGAGGGTCCTGAGACTTGGAATATGGAAGAAGCAATACCCAACC
CCACCAAAGAAAACCTGAGCTTGAAGTCCTTTTCCCCAAAAGAGGGAAGAGTCACAAAAAG
TCCAGACCCCAGGGACGGTACTTTCCCTCTCTACCTGGTGCTCCTCCCTAATGCTCATGAAT
GGACCCCTCATGAATGAAACCAGTGCCCTTATAAGAGACCCCAAAGAGCTGCCTTGCCCTTC
TGCAATGTGTGATCACAGCTAGAAGGCACTGTCAGAGAAGAGAAACTGGTCCTCACCAGATG
CTGAATCTGCTGGTGCCTTGATCTTGGACTTCCCAGCCTCTAGAAGTGTAAAGAAATAAATAT
TTGCTGTTTATAATCCAA

FIGURE 240

MGSSSFVLVLMVSLVLVTLVAVEGVKEGIEKAGVCPADNVRCFKSDPPQCHTDQDCLGERKCC
YLHCGFKCVIPVKELEEGGNKDEDVSRPYPEPGWEAKCPGSSSTRCPQK

FIGURE 241

AAACTCAGCACTTGCCGGAGTGGCTCATTGTTAAGACAAAGGGTGTGCACTTCCTGGCCAGG
AAACCTGAGCGGTGAGACTCCCAGCTGCCTACATCAAGGCCCCAGGACATGCAGAACCTTCC
TCTAGAACCCGACCCACCACTGAGAGTCTGCCTGTGGAGATGCAGGCACCTGAGCCAAGG
CGTCCAGTGGTCTTGCTTCTGGCTGTCTGGTCTTCTTTCTCTTCGCCTTGCCCTCTTTTA
TTAAGGAGCCTCAAACAAAGCCTTCCAGGCATCAACGCACAGAGAACATTAAAGAAAGGTCT
CTACAGTCCCTGGCAAAGCCTAAGTCCCAGGCACCCACAAGGGCGAGGAGGACAACCATCTA
TGCAGAGCCAGCGCCAGAGAACAATGCCCTCAACACACAAACCCAGCCCAAGGCCCACACCA
CCGGAGACAGAGGAAAGGAGGCCAACCCAGGCACCGCCGGAGGAGCAGGACAAGGTGCCCCAC
ACAGCACAGAGGGCAGCATGGAAGAGCCAGAAAAAGAGAAAACCATGGTGAACACACTGTC
ACCCAGAGGGCAAGATGCAGGGATGGCCTCTGGCAGGACAGAGGCACAATCATGGAAGAGCC
AGGACACAAAGACGACCCAAGGAAATGGGGGCCAGACCAGGAAGCTGACGGCCTCCAGGACG
GTGTGAGAGAAGCACCCAGGGCAAAGCGGCAACCACAGCCAAGACGCTCATTCCCAAAAGTCA
GCACAGAATGCTGGCTCCACAGGAGCAGTGTCAACAAGGACGAGACAGAAAGGAGTGACCA
CAGCAGTCATCCACCTAAGGAGAAGAAACCTCAGGCCACCCACCCCTGCCCCCTTTCCAG
AGCCCCACGACGCAGAGAAACCAAGACTGAAGGCCGCCAACTTCAAATCTGAGCCTCGGTG
GGATTTTGAGGAAAAATACAGCTTCGAAATAGGAGGCCTTCAGACGACTTGCCCTGACTCTG
TGAAGATCAAAGCCTCCAAGTCGCTGTGGCTCCAGAAACTCTTTCTGCCCAACCTCACTCTC
TTCTTGACTCCAGACACTTCAACCAGAGTGAGTGGGACCGCCTGGAACACTTTGCACCACC
CTTTGGCTTCATGGAGCTCAACTACTCCTTGGTGCAGAAGGTCGTGACACGCTTCCCTCCAG
TGCCCCAGCAGCAGCTGCTCCTGGCCAGCCTCCCCGCTGGGAGCCTCCGGTGCATCACCTGT
GCCGTGGTGGGCAACGGGGGCATCCTGAACAACTCCACATGGGCCAGGAGATAGACAGTCA
CGACTACGTGTTCCGATTGAGCGGAGCTCTCATTAAAGGCTACGAACAGGATGTGGGGACTC
GGACATCCTTCTACGGCTTTACCGCCTTCTCCCTGACCCAGTCACTCCTTATATTGGGCAAT
CGGGGTTTCAAGAACGTGCCTCTTGGGAAGGACGTCCGCTACTTGCACTTCCTGGAAGGCAC
CCGGGACTATGAGTGGCTGGAAGCACTGCTTATGAATCAGACGGTGATGTCAAAAAACCTTT
TCTGGTTCAGGCACAGACCCAGGAAGCTTTTCGGGAAGCCCTGCACATGGACAGGTACCTG
TTGCTGCACCCAGACTTTCTCCGATACATGAAGAACAGGTTTCTGAGGTCTAAGACCCTGGA
TGGTGCCCACTGGAGGATATACCGCCCCACCACTGGGGCCCTCCTGCTGCTCACTGCCCTTC
AGCTCTGTGACCAGGTGAGTGCTTATGGCTTCACTCACTGAGGGCCATGAGCGCTTTCTGAT
CACTACTATGATACATCATGGAAGCGGCTGATCTTTTACATAAACCATGACTTCAAGCTGGA
GAGAGAAGTCTGGAAGCGGCTACACGATGAAGGGATAATCCGGCTGTACCAGCGTCTGGTC
CCGGAAGTGCCAAAGCCAAGAACTGACCCGGGGCCAGGGCTGCCATGGTCTCCTTGCCCTGCTC
CAAGGCACAGGATACAGTGGGAATCTTGAGACTCTTTGGCCATTTCCCATGGCTCAGACTAA
GCTCCAAGCCCTTCAGGAGTCCAAGGGAACACTTGAACCATGGACAAGACTCTCTCAAGAT
GGCAAATGGCTAATTGAGGTCTGAAGTTCTTCAGTACATTGCTGTAGGTCCTGAGGCCAGG
GATTTTTAATTAAATGGGGTGATGGGTGGCCAATACCACAATTCCTGCTGAAAAACACTCTT
CCAGTCCAAAAGCTTCTTGATACAGAAAAAGAGCCTGGATTACAGAAACATATAGATCTG
GTTTGAATTCCAGATCGAGTTTACAGTTGTGAAATCTTGAAGGTATTACTTAACTTCACTAC
AGATTGTCTAGAAGACCTTTCTAGGAGTTATCTGATTCTAGAAGGGTCTATACTTGTCCTTG
TCTTTAAGCTATTTGACAACTCTACGTGTTGTAGAAAACTGATAATAATACAAATGATTGTT
GTCCATGGAAAGGCAAATAAATTTTCTACAGTGAAAAA

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FIGURE 242

MRSCWRCRHLSQGVQWSLLLAVLVFFLFALPSFIKEPQTKPSRHQRTENIKERSLQSLAKP
KSQAPTRARRTTIYAEPAPENNALNTQTQPKAHTTGDRGKEANQAPPEEQDKVPHTAQRAAW
KSPEKEKTMVNTLSPRGQDAGMASGRTEAQSWKSQDTKTTQGNNGQTRKLTASRTVSEKHQ
KAATTAKTLIPKSQHRMLAPTGA VSTRTRQKGVTTAVIPPEKKPQATPPPAPFQSPTTQRN
QRLKAANFKSEPRWDFEEKYSFEIGGLQTTCPDSVKIKASKSLWLQKLFLPNLTLFLDSRHF
NQSEWDRLEHFAPPPGFMELNYSLVQKVVTTRFPVPQQQLLLASLPAGSLRCITCAVVGNGG
ILNNSHMGQEIDSHDYVFR LSGALIKGYEQDVGTRTSFYGF TAFSLTQSLLILGNRGFKNVP
LGKDVRYLHFLEGTRDYEWLEALLMNQTVMSKNLFWFRHRPQEAFREALHMDRYLLLHPDFL
RYMKNRFLRSKTL DGAHWRIYRPTTGALLLLTALQLCDQVSAYGFITEGHERFSDHYYDTSW
KRLIFYINHDFKLEREVWKRLHDEGIIRLYQRPGPGTAKAKN

FIGURE 243

CGATGCGCGGACCCGGGCACCCCTCCTCCTGGGGCTGCTGCTGGTGCTGGGGCCTTCGCCG
GAGCAGCGAGTGGAAATTGTTTCCTCGAGATCTGAGGATGAAGGACAAGTTTCTAAAACACCT
TACAGGCCCTCTTTATTTTAGTCCAAAGTGCAGCAAACACTTCCATAGACTTTATCACAACA
CCAGAGACTGCACCATTCCTGCATACTATAAAAGATGCGCCAGGCTTCTTACCCGGCTGGCT
GTCAGTCCAGTGTGCATGGAGGATAAGTGAGCAGACCGTACAGGAGCAGCACACCAGGAGCC
ATGAGAAGTGCCTTGGAACCAACAGGGAAACAGAACTATCTTTATACACATCCCCTCATGG
ACAAGAGATTTATTTTTGCAGACAGACTCTTCCATAAGTCCTTTGAGTTTTGTATGTTGTTG
ACAGTTTGCAGATATATATTCGATAAATCAGTGTACTTGACAGTGTTATCTGTCACTTATTT

FIGURE 244

MRGPGHPLLLGLLLVLGPSPEQRVEIVPRDLRMKDKFLKHLTGPLYFSPKCSKHFHRLYHNT
RDCTIPAYYKRCARLLTRLAVSPVCMEDK

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FIGURE 245

GGGCTGGGCCCCGCCGAGCTCCAGCTGGCCGGCTTGGTCCTGCGGTCCCTTCTCTGGGAGG
CCCCGACCCCGGCCGCGCCAGCCCCACCATGCCACCCGCGGGGCTCCGCCGGGCCGCGCCG
CTCACCGCAATCGCTCTGTTGGTGCTGGGGGCTCCCCTGGTGCTGGCCGGCGAGGACTGCCT
GTGGTACCTGGACCGGAATGGCTCCTGGCATCCGGGGTTTAACTGCGAGTTCTTCACCTTCT
GCTGCGGGACCTGCTACCATCGGTACTGCTGCAGGGACCTGACCTTGCTTATCACCGAGAGG
CAGCAGAAGCACTGCCTGGCCTTCAGCCCCAAGACCATAGCAGGCATCGCCTCAGCTGTGAT
CCTCTTTGTTGCTGTGGTTGCCACCACCATCTGCTGCTTCCTCTGTTCTGTTGCTACCTGT
ACCGCCGGCGCCAGCAGCTCCAGAGCCCATTGAAGGCCAGGAGATTCCAATGACAGGCATC
CCAGTGCAGCCAGTATACCCATACCCCCAGGACCCCCAAAGCTGGCCCTGCACCCCCACAGCC
TGGCTTCATGTACCCACCTAGTGGTCCTGCTCCCCAATATCCACTCTACCCAGCTGGGCCCC
CAGTCTACAACCCTGCAGCTCCTCCTCCCTATATGCCACCACAGCCCTCTTACCCGGGAGCC
TGAGGAACCAGCCATGTCTCTGCTGCCCCCTCAGTGATGCCAACCTTGGAAGATGCCCTCAT
CCTGTACCTGCATCTGGTCCTGGGGGTGGCAGGAGTCCTCCAGCCACCAGGCCCCAGACCAA
GCCAAGCCCTGGGCCCTACTGGGGACAGAGCCCCAGGGAAGTGGAACAGGAGCTGAACTAGA
ACTATGAGGGGTGGGGGGAGGGCTTGGAATTATGGGCTATTTTTACTGGGGGCAAGGGAGG
GAGATGACAGCCTGGGTCACAGTGCCTGTTTTCAAATAGTCCCTCTGCTCCCAAGATCCCAG
CCAGGAAGGCTGGGGCCCTACTGTTTGTCCCCTCTGGGCTGGGGTGGGGGGAGGGAGGAGGT
TCCGTCAGCAGCTGGCAGTAGCCCTCCTCTCTGGCTGCCCCACTGGCCACATCTCTGGCCTG
CTAGATTAAAGCTGTAAAGACAAAA

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FIGURE 246

MPPAGLRRAPLTAIALLVLGAPLVLAGEDCLWYLDRNGSWHPGFNCEFFTFCCGTCYHRYC
CRDLTLLITERQQKHCLAFSPKTIAGIASAVILFVAVVATTICCFCLSCCYLYRRRQQLQSP
FEGQEIPMTGIPVQPVYPYPQDPKAGPAPPQPGFMYPSPGPAPQYPLYPAGPPVYNPAAPP
YMPPQPSYPGA

FIGURE 247

GGGGGAGCTAGGCCGCGCGCAGTGGTGGTGGCGCGCGCAAGGGTGAGGGCGGCCCCAGAA
CCCCAGGTAGGTAGAGCAAGAAGATGGTGTCTGCCCCCTCAAATGGTCCCTTGCAACCATG
TCATTTCTACTTTTCTCACTGTTGGCTCTCTTAAGTGTGTCCACTCCTTCATGGTGTGAGAG
CACTGAAGCATCTCCAAAACGTAGTGTGGGACACCATTTCCTTGGAATAAAATACGACTTC
CTGAGTACGTATCCCAGTTCATTATGATCTCTTGATCCATGCAAACCTTACCACGCTGACC
TTCTGGGGAACACGAAAGTAGAAATCACAGCCAGTCAGCCCACCAGCACCATCATCCTGCA
TAGTCACCACCTGCAGATATCTAGGGCCACCCTCAGGAAGGGAGCTGGAGAGAGGCTATCGG
AAGAACCCCTGCAGGTCTTGGAAACCCCCCTCAGGAGCAAATTGCACTGCTGGCTCCCGAG
CCCCTCCTTGTCGGGCTCCCGTACACAGTTGTCACTTCACTATGCTGGCAATCTTTCGGAGAC
TTTCCACGGATTTTACAAAAGCACCTACAGAACCAAGGAAGGGGAAGTGGAGATACTAGCAT
CAACACAATTTGAACCCACTGCAGCTAGAATGGCCTTTCCCTGCTTTGATGAACCTGCCTTC
AAAGCAAGTTTCTCAATCAAATTAGAAGAGAGCCCAAGGCACCTAGCCATCTCCAATATGCC
ATTGGTGAAATCTGTGACTGTTGCTGAAGGACTCATAGAAGACCATTTTGATGTCACTGTGA
AGATGAGCACCTATCTGGTGGCCTTCATCATTTTCAGATTTTGAGTCTGTGAGCAAGATAACC
AAGAGTGGAGTCAAGGTTTCTGTTTATGCTGTGCCAGACAAGATAAATCAAGCAGATTATGC
ACTGGATGCTGCGGTGACTCTTCTAGAATTTTATGAGGATTATTTTCAGCATACCGTATCCCC
TACCCAAACAAGATCTTGCTGCTATTTCCCGACTTTCAGTCTGGTGTATGGAAAAGTGGGGA
CTGACAACATATAGAGAATCTGCTCTGTTGTTGATGCAGAAAAGTCTTCTGCATCAAGTAA
GCTTGGCATCACAGTGAATGCTGGCCCATGAAGTGGCCACCAGTGGTTTGGGAACCTGGTCA
CTATGGAATGGTGGAAATGATCTTTGGCTAAATGAAGGATTTGCCAAATTTATGGAGTTTGTG
TCTGTCACTGTGACCCATCCTGAACTGAAAGTTGGAGATTATTTCTTTGGCAAATGTTTTGA
CGCAATGGAGGTAGATGCTTTAAATTCCTCACACCCTGTGTCTACACCTGTGGAAAATCCTG
CTCAGATCCGGGAGATGTTTGTATGATGTTTCTTATGATAAGGGAGCTTGTATTCTGAATATG
CTAAGGGAGTATCTTAGCGCTGACGCATTTAAAGTGGTATTGTACAGTATCTCCAGAAGCA
TAGCTATAAAAATACAAAAACGAGGACCTGTGGGATAGTATGGCAAGTATTTGCCCTACAG
ATGGTGTAAAAGGGATGGATGGCTTTTGCTCTAGAAGTCAACATTCATCTTCATCCTCACAT
TGGCATCAGGAAGGGGTGGATGTGAAAACCATGATGAACACTTGGACACTGCAGAGGGGTTT
TCCCCTAATAACCATCACAGTGAGGGGGAGGAATGTACACATGAAGCAAGGCACTACATGA
AGGGCTCTGACGGCGCCCCGGACACTGGGTACCTGTGGCATGTTCCATTGACATTCATCACC
AGCAAATCCAACATGGTCCATCGATTTTTGCTAAAAACAAAAACAGATGTGCTCATCCTCCC
AGAAGAGGTGGAATGGATCAAATTTAATGTGGGCATGAATGGCTATTACATTGTGCATTACG
AGGATGATGGATGGGACTCTTTGACTGGCCTTTTAAAGGAACACACACAGCAGTCAGCAGT
AATGATCGGGCAAGTCTCATTAACAATGCATTTTCAGCTCGTCAGCATTTGGGAAGCTGTCCAT
TGAAAAGGCCTTGGATTATCCCTGTACTTGAAACATGAAACTGAAATTATGCCCGTGTTC
AAGGTTTGAATGAGCTGATTCCCTATGTATAAGTTAATGGAGAAAAGAGATATGAATGAAGTG
GAAACTCAATTCAAGGCCTTCCTCATCAGGCTGCTAAGGGACCTCATTGATAAGCAGACATG
GACAGACGAGGGCTCAGTCTCAGAGCAAATGCTGCGGAGTGAAGTACTACTCCTCGCCTGTG
TGCACAACATATCAGCCGTGCGTACAGAGGGCAGAAGGCTATTTTCAGAAAGTGAAGGAATCC
AATGGAACTTGAGCCTGCCTGTGACGCTGACCTTGGCAGTGTGTGCTGTGGGGGCCAGAG
CACAGAAGGCTGGGATTTTCTTTATAGTAAATATCAGTTTTTCTTTGTCCAGTACTGAGAAAA
GCCAAATTGAATTTGCCCTCTGCAGAACCCAAAATAAGGAAAAGCTTCAATGGCTACTAGAT
GAAAGCTTTAAGGGAGATAAAAATAAAACTCAGGAGTTTCCACAAATTTTACACTCATTGG
CAGGAACCCAGTAGGATACCCACTGGCCTGGCAATTTCTGAGGAAAAACTGGAACAACTTG
TACAAAAGTTTGAAGTGGCTCATCTCCATAGCCACATGGTAATGGGTACAACAAATCAA
TTCTCCACAAGAACCGGCTTGAAGAGGTAAAAGGATTCTTCAGCTCTTTGAAAGAAAATGG
TTCTCAGCTCCGTTGTGTCCAACAGACAATTGAAACCATTGAAGAAAACATCGGTTGGATGG
ATAAGAATTTTGATAAAATCAGAGTGTGGCTGCAAAGTGAAGGCTTGAACGTATGTAAAAA
TTCTCCCTTGCCCCGTTTCTGTTATCTCTAATCACCAACATTTTGTGAGTGTATTTTCAA
ACTAGAGATGGCTGTTTTGGCTCCAAGTGGAGATACTTTTTTCCCTTCAACTCATTTTTTGA
CTATCCCTGTGAAAAGAATAGCTGTAGTTTTCATGAATGGGCTTTTTTCATGAATGGGCTA
TCGCTACCATGTGTTTGTTCATCACAGGTGTGCCCTGCAACGTAAACCCAAAGTGTGGGT
TCCCTGCCACAGAAGAATAAAGTACCTTATTCTCTCAAAAAAAGGAAAAAAGGAAAAA

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FIGURE 248

MVFLPLKWSLATMSFLLSSLLALLTVSTPSWCQSTEASPKRSDGTPFPWNKIRLPEYVIPVH
YDLLIHANLTTLTFWGTTKVEITASQPTSTIILHSHHLQISRATLRKGAGERLSEEPLQVLE
HPPQEQIALLAPEPLLVLGLPYTVVIHYAGNLSETFHGFYKSTYRTKEGELRILASTQFEPTA
ARMAFPCFDEPAFKASFSIKIRREPRHLAISNMPLVKSVTVAEGLIEDHFDVTVKMSTYLVA
FIISDFESVSKITKSGVKVSVYAVDPKINQADYALDAAVTLLEFYEDYFSIPYPLPKQDLAA
IPDFQSGAMENWGLTTYRESALLFDAEKSSASSKLGITVTVVAHELHQWFGNLVTMEWWNDL
WLNEGFAKFMEFVSVSVTHPELKVG DYFFGKCFDAMEVDALNSSHPVSTPVENPAQIREMFD
DVSYDKGACILNMLREYLSADAFKSGIVQYLQKHSYKNTKNEDLWDSMASICPTDGVKGMDG
FCSRSQHSSSSSHWHQEGVDVKTMNTWTLQRGFPLITITVRGRNVHMKQEHYMKGSDGAPD
TGYLWHVPLTFITSKSNMVHRFLLKTKTDVLILPEEVEWIKFNVGMNGYYIVHYEDDGWDSL
TGLLKGTHTA VSSNDRASLINNAFQLV SIGKLSIEKALDLSLYLKHETEIMPVFQGLNELIP
MYKLM EK RDMNEVETQFKAF LIRLLRDLIDKQTWTDEGSVSEQMLRSELLLLACVHNYQPCV
QRAEGYFRKWKESNGNLSLPVDVTLAVFAVGAQSTEGWDFLYSKYQFSLSSTEKSQIEFALC
RTQNKEKLQWLLDESFKGDKIKTQEFFQILTILGRNPVGYPLAWQFLRKNWNKLVQKFELGS
SSIAHMMVGT TNQFSTRTRLEEVKGFFSSLKENGSQLRCVQQT IETIEENIGWMDKNFDKIR
VWLQSEKLERM

FIGURE 249

CAGCCACAGACGGGTCATGAGCGCGGTATTACTGCTGGCCCTCCTGGGGTTCATCCTCCAC
TGCCAGGAGTGCAGGCGCTGCTCTGCCAGTTTGGGACAGTTCAGCATGTGTGGAAGGTGTCC
GACCTACCCCGGCAATGGACCCCTAAGAACACCAGCTGCGACAGCGGCTTGGGGTGCCAGGA
CACGTTGATGCTCATTGAGAGCGGACCCCAAGTGAGCCTGGTGCTCTCCAAGGGCTGCACGG
AGGCCAAGGACCAGGAGCCCCGCGTCACTGAGCACCGGATGGGCCCCGGCCTCTCCCTGATC
TCCTACACCTTCGTGTGCCGCCAGGAGGACTTCTGCAACAACCTCGTTAACTCCCTCCCGCT
TTGGGCCCCACAGCCCCCAGCAGACCAGGATCCTTGAGGTGCCAGTCTGCTTGTCTATGG
AAGGCTGTCTGGAGGGGACAACAGAAGAGATCTGCCCCAAGGGGACCACACACTGTTATGAT
GGCCTCCTCAGGCTCAGGGGAGGAGGCATCTTCTCCAATCTGAGAGTCCAGGGATGCATGCC
CCAGCCAGGTTGCAACCTGCTCAATGGGACACAGGAAATTGGGCCCCGTGGGTATGACTGAGA
ACTGCAATAGGAAAGATTTTCTGACCTGTCATCGGGGGACCACCATTATGACACACGGAAAC
TTGGCTCAAGAACCCACTGATTGGACCACATCGAATACCGAGATGTGCGAGGTGGGGCAGGT
GTGTCAGGAGACGCTGCTGCTCATAGATGTAGGACTCACATCAACCCTGGTGGGGACAAAAG
GCTGCAGCACTGTTGGGGCTCAAAATTCCCAGAAGACCACCATCCACTCAGCCCCCTCCTGGG
GTGCTTGTGGCCTCCTATACCCACTTCTGCTCCTCGGACCTGTGCAATAGTGCCAGCAGCAG
CAGCGTTCTGCTGAACTCCCTCCCTCCTCAAGCTGCCCCCTGTCCCAGGAGACCGGCAGTGTC
CTACCTGTGTGCAGCCCCCTTGGAACCTGTTCAAGTGGCTCCCCCGAATGACCTGCCCCAGG
GGCGCCACTCATTGTTATGATGGGTACATTCATCTCTCAGGAGGTGGGCTGTCCACCAAAAT
GAGCATTGAGGGCTGCGTGGCCCAACCTTCCAGCTTCTTGTTGAACCACACCAGACAAATCG
GGATCTTCTCTGCGCGTGAGAAGCGTGATGTGCAGCCTCCTGCCTCTCAGCATGAGGGAGGT
GGGGCTGAGGGCCTGGAGTCTCTCACTTGGGGGGTGGGGCTGGCACTGGCCCCAGCGCTGTG
GTGGGGAGTGGTTTGCCCTTCCTGCTTAACTCTATTACCCCCACGATTCTTCACCGCTGCTGA
CCACCCACACTCAACCTCCCTCTGACCTCATAACCTAATGGCCTTGACACCAGATTCTTTTC
CCATTCTGTCCATGAATCATCTTCCCCACACACAATCATTATATCTACTCACCTAACAGCA
ACACTGGGGAGAGCCTGGAGCATCCGGAATTGCCCTATGGGAGAGGGGACGCTGGAGGAGTG
GCTGCATGTATCTGATAATACAGACCCTGTCCTTTCA

FIGURE 250

MSAVLLLALLGFILPLPGVQALLCQFGTVQHVWKVSDLPRQWTPKNTSCDSGLGCQDTLMLI
ESGPQVSLVLSKGCTEAKDQEPRVTEHRMGPGLSLISYTFVCRQEDFCNNLVNSLPLWAPQP
PADPGSLRCPVCLSMEGCLEGTTEEICPKGTTHCYDGLLRRLRGGGIFSNLRVQGCMPPQPGCN
LLNGTQEIGPVGMTENCNRKDFLTCHRGTTIMTHGNLAQEPTDWTTSENTEMCEVGQVCQETL
LLIDVGLTSTLVGTKGCSTVGAQNSQKTTIHSAPPGVLVASYTHFCSSDLCNSASSSSVLLN
SLPPQAAPVPGDRQCPTCVQPLGTCSSGSPRMTCPRGATHCYDGYIHLSGGGLSTKMSIQGC
VAQPSSFLLNHTRQIGIFSAREKRDVQPPASQHEGGGAEGLES LTWGVGLALAPALWWGVVCPSC

FIGURE 251

GCGACGGGCAGGACGCCCCGTTTCGCCTAGCGCGTGCTCAGGAGTTGGTGTCTCTGCCTGCGCT
CAGGATGAGGGGGAATCTGGCCCTGGTGGGCGTTCTAATCAGCCTGGCCTTCCTGTCACTGCTG
CCATCTGGACATCCTCAGCCGGCTGGCGATGACGCCTGCTCTGTGCAGATCCTCGTCCCTGG
CCTCAAAGGGGATGCGGGAGAGAAGGGAGACAAAGGCGCCCCCGGACGGCCTGGAAGAGTCG
GCCCCACGGGAGAAAAAGGAGACATGGGGGACAAAGGACAGAAAGGCAGTGTGGGTCTCAT
GGAAAAATTGGTCCCATTGGCTCTAAAGGTGAGAAAGGAGATTCCGGTGACATAGGACCCCC
TGGTCCTAATGGAGAACCAGGCCTCCCATGTGAGTGCAGCCAGCTGCGCAAGGCCATCGGGG
AGATGGACAACCAGGTCTCTCAGCTGACCAGCGAGCTCAAGTTCATCAAGAATGCTGTGCC
GGTGTGCGCGAGACGGAGAGCAAGATCTACCTGCTGGTGAAGGAGGAGAAGCGCTACGCGGA
CGCCAGCTGTCCTGCCAGGGCCGCGGGGGCACGCTGAGCATGCCCAAGGACGAGGCTGCCA
ATGGCCTGATGGCCGCATACCTGGCGCAAGCCGGCCTGGCCCGTGTCTTCATCGGCATCAAC
GACCTGGAGAAGGAGGGCGCCTTCGTGTACTCTGACCACTCCCCCATGCGGACCTTCAACAA
GTGGCGCAGCGGTGAGCCCAACAATGCCTACGACGAGGAGGACTGCGTGGAGATGGTGGCCT
CGGGCGGCTGGAACGACGTGGCCTGCCACACCACCATGTACTTCATGTGTGAGTTTGACAAG
GAGAACATGTGAGGCCTCAGGCTGGGGCTGCCATTGGGGGCCCCACATGTCCCTGCAGGGTT
GGCAGGGACAGAGCCCAGACCATGGTGCCAGCCAGGGAGCTGTCCCTCTGTGAAGGGTGGAG
GCTCACTGAGTAGAGGGCTGTTGTCTAAACTGAGAAAATGGCCTATGCTTAAGAGGAAAATG
AAAGTGTTCCCTGGGGTGCTGTCTCTGAAGAAGCAGAGTTTCATTACCTGTATTGTAGCCCCA
ATGTCATTATGTAATTATTACCCAGAATTGCTCTTCATAAAGCTTGTGCCTTTGTCCAAGC
TATACAATAAAATCTTTAAGTAGTGCAGTAGTTAAGTCCAAAAAAAAAAAAAAAAAAAAA

FIGURE 252

MRGNLALVGVLISLAFLSLLPSGHPQPAGDDACSVQILVPGLKGDAGEKGDKGAPGRPGRVG
PTGEKGDMDKGQKGSVGRHGKIGPIGSKGEKGDSDIGPPGPNGEPLPCECSQLRKAIGE
MDNQVSQLTSELKFIKNAVAGVRETESKIYLLVKEEKRYADAQLSCQGRGGTLSMPKDEAAN
GLMAAYLAQAGLARVFIGINDLEKEGAFVYSDHSPMRTFNKWRSGEPNNAYDEEDCVEMVAS
GGWNDVACHTTMYFMCEFDKENM

FIGURE 253

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTGCAGGAGCACCGGCAG
CACCAGTGTGTGAGGGGAGCAGGCAGCGGTCTAGCCAGTTCCTTGATCCTGCCAGACCACC
CAGCCCCCGGCACAGAGCTGCTCCACAGGCACCATGAGGATCATGCTGCTATTCACAGCCAT
CCTGGCCTTCAGCCTAGCTCAGAGCTTTGGGGCTGTCTGTAAGGAGCCACAGGAGGAGGTGG
TTCCTGGCGGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCAGAGACTCTTC
AAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAGCACAGATCCTAA
GGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGGACTTATGGGCAAGA
GGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGTGAGGGTTCCTCGGCCC
CTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGGAACAGAGGAGCAGAGACC
TTTATATAAGACTCTCCTACGGATGTGAATCAAGAGAACGTCCCCAGCTTTGGCATCCTCAAGT
ATCCCCCGAGAGCAGAATAGGTACTCCACTTCCGGACTCCTGGACTGCATTAGGAAGACCTC
TTTCCCTGTCCCAATCCCCAGGTGCGCACGCTCCTGTTACCCTTTCTCTTCCCTGTTCTTGT
AACATTCTTGCTTTGACTCCTTCTCCATCTTTTCTACCTGACCCTGGTGTGGAAACTGCA
TAGTGAATATCCCCAACCCCAATGGGCATTGACTGTAGAATACCCTAGAGTTCTGTAGTGT
CCTACATTAAAAATATAATGTCTCTCTCTATTCTCAACAATAAAGGATTTTTGCATATGAA
AA

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FIGURE 254

MRIMLLFTAILAFSLAQSFQAVCKEPQEEVVPGGGRSKRDPDLYQLLQRLFKSHSSLEGLLK
ALSQASTDPKESTSPEKRDHDFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLGSTGK
SSLGTEEQRPL

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FIGURE 255

GGGCGTCTCCGGCTGCTCCTATTGAGCTGTCTGCTCGCTGTGCCCCTGTGCCTGCTGTGCC
CGCGCTGTGCGCGCTGCTACCGCGTCTGCTGGACGCGGGAGACGCCAGCGAGCTGGTGATTG
GAGCCCTGCGGAGAGCTCAAGCGCCCAGCTCTGCCCCAGGAGCCCAGGCTGCCCCGTGAGTC
CCATAGTTGCTGCAGGAGTGGAGCCATGAGCTGCGTCCTGGGTGGTGTATCCCCCTGGGGC
TGCTGTTCTTGGTCTGCGGATCCCAAGGCTACCTCCTGCCCAACGTCACTCTCTTAGAGGAG
CTGCTCAGCAAATACCAGCACAACGAGTCTCACTCCCGGTCCGCAGAGCCATCCCCAGGGA
GGACAAGGAGGAGATCCTCATGCTGCACAACAAGCTTCGGGGCCAGGTGCAGCCTCAGGCCT
CCAACATGGAGTACATGGTGAGCGCCGGCTCCGGCCGCAGAGGCTGGCACCGGGGGTGGGGC
CTGGGCCACCAGCCTGCTCTGTTCCCCAGCCAGCTCTGTTCCCCAGCCAGTGCGTGTGATGG
CTGGCTCAGGGTCTCCTCTGGCAGGGGAGGATCCCGGCTCTGTTCTGTTTTGTTTGTGTTGTT
TTGAGACAGGGTCTCACTCTGCCACTGACGCTGGAGTGCAATGGCACAATCGTCATGCCCTG
AAACCTTAGACTCCCGGGGTTAAGCGATCCTGCTTCAGCCTCCCAAGTAGCTGGAACCTACAG
GCATGCACCATGGTGCCAGCTAGATTTTAAATATTTTGTGGAGATGGGGGTCTTGCTACGT
TGCCCAGGCTGGTCTTGAACTCCTAGGCTCAAGCAATCCTCCTGCCTCAGCCTCTCAAAGTG
CTAGGATTATAGGCATGAGTCACCCTGTCTGGCTCTGGCTCTGTTCTTAACATTCTGCCAAA
ACAACACACGTGGGTTCCTGTGCAGAGCCTGCCTCGTTGCCTTCATGTCACTCTTGGTAGC
TCCACTGGGAACACAGCTCTCAGCCTTTCCACCTGGAGGCAGAGTGGGGAGGGGCCCAGGG
CTGGGCTTTGCTGATGCTGATCTCAGCTGTGCCACACGCTAGCTGCACCACCCTGACTTCTC
CTTAGCCCGTGTGAGCCTCACTTTCCACTTGGAGAGTCCTTCCTCGCGTGGTTGCCATGACT
GTGAGATAAGTCGAGGCTGTGAAGGGCCCGGCACAGACTGACCTGCCTCCCCAACCCCTAGG
CTTTGCTAACC GGGAAGGAGCTAACGGTGACAGAAGACAGCCAAGGTCAACCCTCCCGGGT
GATTGTGATGGGTGTTCCAGGTGTGGTTGGGCGATGCTGCTACTTGACCCCAAGCTCCAGTG
TGGAACCTTCCTTCCTGGCTGGTTTTCCAGAACTACAGAGGAATGGACCACAGTCTTCCAGG
GTCCCTCCTCGTCCACCAACCGGAGCCTCCACCTTGGCCATCCGTGAGCTATGAATGGCTT
TTTAAACAAACCCACGTCCCAGCCTGGGTAAACATGGTAAAGCCCCGTCTCTACAAAAAATC
CAAGTTAGCCGGGCATGGTGGTGCGCACCTGTAGTCCCAGCTGCAGTGGGACTGAGGTGGAG
GTGGAGGTGGGGGGTGGGAGCTGAGGAAGGAGGATCGCTTGAGCCTGGGAAGTCGAGGCTGC
AGTGAGCTGAGATTGCACCACTGCACTCCAGCCTGGGTGACAGAGCAAGACCCCTGTCTCAAAA

FIGURE 256

MSCVLGGVIPLGLLFLVCGSQGYLLPNVTLLLEELLSKYQHNEHSRVRRRAIPREDKEEILML
HNKLRGQVQPQASNMEYMVSAGSGRRGWHRGWGLGHQPALFPSQLCSPASACDGWLRVSSGR
GGSRLCSVLFVCFETGSHSATDAGVQWHNRHALKP

FIGURE 257

AAGGAGAGGCCACCGGGACTTCAGTGTCTCCTCCATCCCAGGAGCGCAGTGGCCACTATGGG
GTCTGGGCTGCCCCCTTGTCTCCTCTTGACCCTCCTTGGCAGCTCACATGGAACAGGGCCGG
GTATGACTTTGCAACTGAAGCTGAAGGAGTCTTTTCTGACAAATTCCTCCTATGAGTCCAGC
TTCCTGGAATTGCTTGAAAAGCTCTGCCTCCTCCTCCATCTCCCTTCAGGGACCAGCGTCAC
CCTCCACCATGCAAGATCTCAACACCATGTTGTCTGCAACACATTGACAGCCATTGAAGCCTG
TGTCTTCTTGGCCCGGGCTTTTGGGCCGGGGATGCAGGAGGCAGGCCCGACCCCTGTCTTT
CAGCAGGCCCCCACCTCCTGAGTGGCAATAAATAAAATTCGGTATGCTG

FIGURE 258

MGSGPLVLVLLLTLLGSSHGTGPGMTLQKLKESFLTNSSYESSFLELLEKLCLLLHLPSGTS
VTLHHARSQHHVVCNT

FIGURE 259

AATTGTATCTGTGTAATGTTAAAACAAACGAAATAAAATAGAAGGAAAACTTTCTGAGTTT
CAAAAACAACAGACTAGTACTCTAAAGAACTCTTTAAAACAATTAAGTGTAGGATTGCAGT
TATGATTGGATATTATTTAATTCTGTTTCTGATGTGGGGTTCCTCCACTGTGTTCTGTGTGC
TATTAATATTTACCATTGCAGAAGCTTCATTCAGTGTTGAAAATGAATGCTTAGTGGATCTG
TGCTCTTACGCATATGTTACAAATTATCTGGAGTTCCTAATCAATGCAGAGTTCCCCCTCCC
CTCCGATTGTTCTAAATTAATTGAAAGATGTCTGCTGTGGAAAAAGGCATGTATTTAAATCTG
TATGATTCTCAACCATCTTTAGTTGGGAAAGGTCCTTGAAAGCCAATGGAAATACTTTTTTT
TTTTCTTGGCACTAATCAAGTGAGTGTTACCTTTTCACTTAGTAGGATGTGTTGTTACGCTA
GTAAAATAGAAACCTGTGTTTATTCTCAGGTATTTTAGAAACAACAGCCATCATTTTATTTT
ATGTGTGTGTTCTTGGCTGTATTCATAAATTATATATTTTGGGCTATCAAATATTACTTCAT
TCAATATAAATAACAATAGTAGAAGTTGTTTACTTAGATATGCTTTCTAGTTGCATTTTCTC
AGCCTATGTAAGACTACTTTGTTGTAATAGCCTTTGAAATTACAGTACTGTCTCTCTACTA
TCTTCAGATTACTTGATTCAAATAAACCAATTATGTTTGTAATTGATATTAATAAAACCAGA
ATAAAAGTTCATATCTACCC

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FIGURE 260

MIGYYLILFLMWGSSTVFCVLLIFTIAEASFVENECLVDLCLLRICYKLSGVPNQCRVPLP
SDCSK

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FIGURE 261

GAGGATTTGCCACAGCAGCGGATAGAGCAGGAGAGCACCACCGGAGCCCTTGAGACATCCTT
GAGAAGAGCCACAGCATAAGAGACTGCCCTGCTTGGTGT TTTGCAGGATGATGGTGGCCCTT
CGAGGAGCTTCTGCATTGCTGGTTCTGTTCCTTGACGCTTTTCTGCCCCCGCCGAGTGTAC
CCAGGACCCAGCCATGGTGCATTACATCTACCAGCGCTTTCGAGTCTTGAGCAAGGGCTGG
AAAAATGTACCCAAGCAACGAGGGCATAACATTCAAGAATTCCAAGAGTTCTCAAAAAATATA
TCTGTCTATGCTGGGAAGATGT CAGACCTACACAAGTGAGTACAAGAGTGCAGTGGGTAACCTT
GGCACTGAGAGTTGAACGTGCCCAACGGGAGATTGACTACATAACAATACCTTCGAGAGGCTG
ACGAGTGCATCGTATCAGAGGACAAGACACTGGCAGAAATGTTGCTCCAAGAAGCTGAAGAA
GAGAAAAAGATCCGGACTCTGCTGAATGCAAGCTGTGACAACATGCTGATGGGCATAAAGTC
TTTGAAAATAGTGAAGAAGATGATGGACACACATGGCTCTTGATGAAAGATGCTGTCTATA
ACTCTCCAAAGGTGTACTTATTAATTGGATCCAGAAACAACACTGTTTGGGAATTTGCAAAC
ATACGGGCATTTCATGGAGGATAACACCAAGCCAGCTCCCCGGAAGCAAATCCTAACACTTTC
CTGGCAGGGAACAGGCCAAGTGATCTACAAAGGTTTTCTATTTTTTCATAACCAAGCAACTT
CTAATGAGATAATCAAATATAACCTGCAGAAGAGGACTGTGGAAGATCGAATGCTGCTCCCA
GGAGGGGTAGGCCGAGCATTGGTTTTACCAGCACTCCCCCTCACTTACATTGACCTGGCTGT
GGATGAGCATGGGCTCTGGGCCATCCACTCTGGGCCAGGCACCCATAGCCATTTGGTTCTCA
CAAAGATTGAGCCGGGCACACTGGGAGTGGAGCATTTCATGGGATACCCCATGCAGAAGCCAG
GATGCTGAAGCCTCATTCTTGTGTGGGTTCTCTATGTGGTCTACAGTACTGGGGGCCA
GGGCCCTCATCGCATCACCTGCATCTATGATCCACTGGGCATATCAGTGAGGAGGACTTGC
CCAACCTGTTCTTCCCCAAGAGACCAAGAAGTCACTCCATGATCCATTACAACCCAGAGAT
AAGCAGCTCTATGCCTGGAATGAAGGAAACAGATCATTACAAACTCCAGACAAAGAGAAA
GCTGCCTCTGAAGTAAATGCATTACAGCTGTGAGAAAGAGCACTGTGGCTTTGGCAGCTGTTT
TACAGGACAGTGAGGCTATAGCCCCTTCACAATATAGTATCCCTCTAATCACACACAGGAAG
AGTGTGTAGAAGTGGAATACGTATGCCTCCTTTCCCAAATGTCACCTGCCTTAGGTATCTTC
CAAGAGCTTAGATGAGAGCATATCATCAGGAAAGTTTTCAACAATGTCCATTACTCCCCAAA
CCTCCTGGCTCTCAAGGATGACCACATTCTGATACAGCCTACTTCAAGCCTTTTGT TTTTACT
GCTCCCCAGCATTTACTGTAACTCTGCCATCTTCCCTCCCAATTAGAGTTGTATGCCAGC
CCCTAATATTACCACTGGCTTTTCTCTCCCTGGCCTTTGCTGAAGCTCTTCCCTCTTTTT
CAAATGTCTATTGATATTCTCCCATTTTCACTGCCCAACTAAAATACTATTAATATTTCTTT
CTTTTCTTTTCTTTTTTTTGAGACAAGGTCTCACTATGTTGCCAGGCTGGTCTCAAACCTCC
AGAGCTCAAGAGATCCTCCTGCCTCAGCCTCCTAAGTACCTGGGATTACAGGCATGTGCCAC
CACACCTGGCTTAAAATACTATTTCTTATTGAGGTTTAACTCTATTTCCCCTAGCCCTGTC
CTTCCACTAAGCTTGGTAGATGTAATAATAAAGTGAAAATATTAACATTTGAATATCGCTTT
CCAGGTGTGGAGTGTTTGACATCATTGAATTCTCGTTTCACCTTTGTGAAACATGCACAAG
TCTTTACAGCTGTCATTCTAGAGTTTAGGTGAGTAACACAATTACAAAGTGAAAGATACAGC
TAGAAAATACTACAAATCCCATAGTTTTTCCATTGCCCAAGGAAGCATCAAATACGTATGTT
TGTTTCACCTACTCTTATAGTCAATGCGTTTCATCGTTTCAGCCTAAAAATAATAGTCTGTCCC
TTTAGCCAGTTTTTCATGTCTGCACAAGACCTTCAATAGGCCTTTCAAATGATAATTCTCC
AGAAAACCAGTCTAAGGGTGAGGACCCCAACTCTAGCCTCCTCTTGTCTTGCTGTCTCTGT
TTCTCTCTTTCTGCTTTAAATTCAATAAAAGTGACACTGAGCAAAAAAAAAAAAAA

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FIGURE 262

MMVALRGASALLVLFLAAFLPPPQCTQDPAMVHYIYQRFRLVLEQGLEKCTQATRAYIQEFQE
FSKNISVMLGRCQTYTSEYKSAVGNLALRVERAQREIDYIQYLREADECIVSEDKTLAEMLL
QEAEKKKIRTLLNASCDNMLMGIKSLKIVKKMMDTHGSWMKDAVYNPKVYLLIGSRNNTV
WEFANIRAFMEDNTKPAPRKQILTLSWQGTGQVIYKGFLFFHNQATSNEIIKYNLQKRTVED
RMLLPGGVGRALVYQHSPSTYIDLAVDEHGLWAIHSGPGTHSHLVLTKEPPTLGVEHSWDT
PCRSQDAEASFLLCGVLYVVYSTGGQGPHRITCIYDPLGTISEEDLPNLFFPKRPRSHSMIH
YNPRDKQLYAWNEGNQIIYKLQTKRKLPLK

[illegible]

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FIGURE 264

MELSQMSELMGLSVLLGLLALMATAAVARGWLRAGEERSGRPACQKANGFPPDKSSGSKKQK
QYQRIRKEKPQQHNFTHRLLAAALKSHSGNISCMDFSSNGKYLATCADDRTIRIWSTKDFLQ
REHRSMRANVELDHATLVRFPSPDCRAFI VWLANGDTLRVFKMTKREDGGYTFTATPEDFPKK
HKAPVIDIGIANTGKFIMTASSDTTVLIWSLKQVLTINTNQMNNTAAVSPCGRFVASCG
FTPDVKVWEVCFGKKGEFQEVVRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWKLWDTDV
EYKKKQDPYLLKTGRFEEAAGAAPCRLALSPNAQVLALASGSSIHLYNTRRGEKEECFERVH
GECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAMVEEMQGHLKRASNESTRQRLQQQLTQ
AQETLKS LGALKK

FIGURE 265

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCAGG
CAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTGCCACGCGAGTCTCAATCATGCTCC
TCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTCCAGTGT
GGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGCACCCCGCT
GGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTCAGGAAACGCA
AGCACCACACCTGTCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCGGACGGCAGGTAC
CGCTGCTCCATGGACTTGAAGAACATCAATTTTTTAGGCGCTTGCCTGGTCTCAGGATACCCA
CCATCCTTTTCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAAACCCAGCTCCCATGAC
TCTCCCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGTACGCACATATGCACACAG
GCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCTGAGGATGTACAGCTTGAGG
CTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGCTCAGGCTGCCAGAGAGGTGGTA
AATGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTGACCTGCTCTCTTTCTGGGCCCTG
CCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAGACATTCTTGGGCACAGGCTCTTGGGT
GCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCCTCAGGCCCTTCACGTGAGGTCTGTGAGG
ACCAATTTGTGGGTAGTTCATCTTCCCTCGATTGGTTAACTCCTTAGTTTCAGACCACAGAC
TCAAGATTGGCTCTTCCCAGAGGGCAGCAGACAGTCACCCCAAGGCAGGTGTAGGGAGCCCA
GGGAGGCCAATCAGCCCCCTGAAGACTCTGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGA
CCTGTGACCTTCTGCCAGAATTGTCATGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGT
TAACCACTGAAGCCCCCAATTCCCACAGCTTTTCATTAAATGCAAATGGTGGTGGTTCAA
TCTAATCTGATATTGACATATTAGAAGGCAATTAGGGTGTTCCTTAAACAACTCCTTTCCA
AGGATCAGCCCTGAGAGCAGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGG
TGGGAGCAAGGGACAGGGAGCAGGGCAGGGGCTGAAAGGGGCACTGATTCAGACCAGGGAGG
CAACTACACACCAACATGCTGGCTTTAGAATAAAAGCACCAACTGAAAAA

FIGURE 266

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAI SLWLRGLRMCTPLGREGE ECHP
GSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

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FIGURE 267

AGCGCCCGGGCGTCGGGGCGGTAAAAGGCCGGCAGAAGGGAGGCACTTGAGAAATGTCTTTC
CTCCAGGACCCAAGTTTCTTCACCATGGGGATGTGGTCCATTGGTGCAGGAGCCCTGGGGGC
TGCTGCCTTGGCATTGCTGCTTGCCAACACAGACGTGTTTCTGTCCAAGCCCCAGAAAGCGG
CCCTGGAGTACCTGGAGGATATAGACCTGAAAACACTGGAGAAGGAACCAAGGACTTTCAAA
GCAAAGGAGCTATGGGAAAAAAATGGAGCTGTGATTATGGCCGTGCGGAGGCCAGGCTGTTT
CCTCTGTGCGAGAGGAAGCTGCGGATCTGTCTCCCTGAAAAGCATGTTGGACCAGCTGGGCG
TCCCCCTCTATGCAGTGGTAAAGGAGCACATCAGGACTGAAGTGAAGGATTTCCAGCCTTAT
TTCAAAGGAGAAATCTTCCTGGATGAAAAGAAAAAGTTCTATGGTCCACAAAGGCGGAAGAT
GATGTTTATGGGATTTATCCGTCTGGGAGTGTGGTACAACCTTCTTCCGAGCCTGGAACGGAG
GCTTCTCTGGAACCTGGAAGGAGAAGGCTTCATCCTTGGGGGAGTTTTCGTGGTGGGATCA
GGAAAGCAGGGCATTCTTCTTGAGCACCGAGAAAAAGAATTTGGAGACAAAGTAAACCTACT
TTCTGTTCTGGAAGCTGCTAAGATGATCAAACCACAGACTTTGGCCTCAGAGAAAAAATTGAT
TGTGTGAAACTGCCCAGCTCAGGGATAACCAGGGACATTCACCTGTGTTTCATGGGATGTATT
GTTTCCACTCGTGTCCCTAAGGAGTGAGAAACCCATTTATACTCTACTCTCAGTATGGATTA
TTAATGTATTTTAATATTCTGTTTAGGCCCACTAAGGCAAATAGCCCCAAAACAAGACTGA
CAAAAATCTGAAAACTAATGAGGATTATTAAGCTAAAACCTGGGAAATAGGAGGCTTAAAA
TTGACTGCCAGGCTGGGTGCAGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCAAGG
TGAGCAAGTCACTTGAGGTCGGGAGTTCGAGACCAGCCTGAGCAACATGGCGAAACCCCGTC
TCTACTAAAAATACAAAATCACCCGGGTGTGGTGGCAGGCACCTGTAGTCCCAGCTACCCG
GGAGGCTGAGGCAGGAGAATCACTTGAACCTGGGAGGTGGAGGTTGCGGTGAGCTGAGATCA
CACCACTGTATTCAGCCTGGGTGACTGAGACTCTAACTAA

FIGURE 268

MSFLQDPSFFTGMWSIGAGALGAAALALLLANTDVFLSKPQKALEYLEDIDLKTLEKEPR
TFKAKELWEKNGAVIMAVRRPGCFLCREEAADLSSLKSMLDQLGVPLYAVVKEHIRTEVKDF
QPYFKGEIFLDEKKKFYGPQRRKMMFMGFIRLGWYNFFRAWNGGFSGNLEGEFGFILGGVFV
VGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK

FIGURE 269

ACGGACCGAGGGTTCGAGGGAGGGACACGGACCAGGAACCTGAGCTAGGTCAAAGACGCCCC
GGCCAGGTGCCCCGTCGCAGGTGCCCCCTGGCCGGAGATGCGGTAGGAGGGGCGAGCGCGAGA
AGCCCCTTCCTCGGCGCTGCCAACCCGCCACCCAGCCCCATGGCGAACCCCGGGCTGGGGCTG
CTTCTGGCGCTGGGCCTGCCGTTCTTGCTGGCCCCGCTGGGGCCGAGCCTGGGGGCAAATACA
GACCACTTCTGCAAATGAGAATAGCACTGTTTTGCCTTCATCCACCAGCTCCAGCTCCGATG
GCAACCTGCGTCCGGAAGCCATCACTGCTATCATCGTGGTCTTCTCCCTCTTGGCTGCCTTG
CTCCTGGCTGTGGGGCTGGCACTGTTGGTGCGGAAGCTTCGGGAGAAGCGGCAGACGGAGGG
CACCTACCGGCCCAGTAGCGAGGAGCAGTTCTCCCATGCAGCCGAGGCCCGGGCCCCCTCAGG
ACTCCAAGGAGACGGTGCAGGGCTGCCTGCCCATCTAGGTCCCCTCTCCTGCATCTGTCTCC
CTTCATTGCTGTGTGACCTTGGGGAAAGGCAGTGCCCTCTCTGGGCAGTCAGATCCACCCAG
TGCTTAATAGCAGGGAAGAAGGTACTTCAAAGACTCTGCCCCTGAGGTCAAGAGAGGATGGG
GCTATTCACCTTTTATATATTTATATAAAATTAGTAGTGAGATGTAAAAAAAAAAAAAAAAAAAA

FIGURE 270

MANPGLGLLLALGLPFLARWGRAWGQIQTTSANENSTVLPSTSSSSDGNLRPEAITAIIV
VFSLLAALLLAVGLALLVRKLREKRQTEGTYRPSSEEQFSHAAEARAPQDSKETVQGCLPI

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FIGURE 271

AATATATCATCTATTTATCATTAATCAATAATGTATTCTTTTATTCCAATAACATTTGGGTT
TTGGGATTTTAATTTTCAAACACAGCAGAAATGACATTTTTTCTGTCACTATTATTATTGTTG
GTATGTGAAGCTATTTGGAGATCCAATTCAGGAAGCAACACATTGGAGAATGGCTACTTTCT
ATCAAGAAATAAAGAGAACCACAGTCAACCCACACAATCATCTTTAGAAGACAGTGTGACTC
CTACCAAAGCTGTCAAAACCACAGGCAAGGGCATAGTTAAAGGACGGAATCTTGACTCAAGA
GGGTTAATTCTTGCTGCTGAAGCCTGGGGCAGGGGTGTAAAGAAAAACACTTAGATTCAATG
ATTGTAAATTTAAGGCAAATACACATATTAGTATTACCTTAGTGTAATGTATCCCTGTCATA
TATACAATAAGGTGAAATTATAAGTACCCTATGCAGTTGGCTGGACAGTTCTAAATTGGACT
TTATTAATTTTAAAATCAGTAACTGATTATCACTGGCTATGTGCTTAGATCTACAGGAGA
TCATATAATTTGATACAAATAAAAGAAAAGTGTCTCTCCCCTTACAGAATTGACATTTTAA
ATGCGATACAGTTAGAATAGGAAATATGACATTAGAAAGGAAGAATGACAGGGAGAAAGGAA
AGAAGGGAAAATGTTGCCAAGGAAAAA

FIGURE 272

MTFFLSLLLLLVCEAIWRSNSGSNTLENGYFLSRNKENHSQPTQSSLEDSVTPTKAVKTTGK
GIVKGRNLDSRGLILGAEAWGRGVKKNT

FIGURE 273

[illegible]

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FIGURE 274

MGLFRGFVFLLVLCLLHQSNTSFIKLNNNGFEDIVIVIDPSVPEDEKIEQIEDMVTASTY
LFEATEKRFFFKNVSILIPENWKENPOYKRPKHENHKHADVIVAPPTLPGRDEPYTKQFTEC
GEKGEYIHFTPDLLLGGKQNEYGPPGKLFVHEWAHLRWGVFDEYNEDQPFYRAKSKKIEATR
CSAGISGRNRVYKCQGGSCLSRACRIDSTTKLYGKDCQFFPDQVQTEKASIMFMQSIDSVVE
FCNEKTHNQEAPSLQNIKCNFRSTWEVISNSEDFKNTIPMVTPPPPPVFSLKISQRIVCLV
LDKSGSMGGKDRLNRMNQAAKHFLQTVENGSWVGMVHFDSTATIVNKLIQIKSSDERNTLM
AGLPTYPLGGTSCSGIKYAFQVIGELHSQLDGSEVLLLLTDGEDNTASSCIDEVKQSGAIVH
FIALGRAADEAVIEMSKITGGS HFYVSDEAQNNGLIDAFGALTSGNTDLSQKSLQLESKGLT
LNSNAWMNDTVIIDSTVGKDTFFLITWNSLPPSISLWDPSGTIMENFTVDATSKMAYLSIPG
TAKVGTWAYNLQAKANPETLTITVTSRAANSSVPPITVNAKMNKDVNSFPSPMIVYAEILQG
YVPVLGANVTAFIESQNGHTEVLELLDNGAGADSFKN DGVYSRYFTAYTENGRYSLKVBRAHG
GANTARLKLRPPLNRAAYIPGWVVNGEIEANPPRPEIDEDTQTTLEDFSR TASGGAFVVSQV
PSLPLPDQYPPSQITDLDATVHEDKIILTWTAPGDNFDVGKVQRYIIRISASILDLRDSFDD
ALQVNTTDLSPKEANSKESFAFKPENISEENATHIFIAIKSIDKSNLTSKVS NIAQVTLFIP
QANPDDIDPTPTPTPTPTPDKSHNSGVNISTLVLSVIGSVVIVNFILSTTI

TCCTCTTAGGTGGAAACCTCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATACGTCCCCGGC
GCAGGGGTGACAACAGGTGT CATCTTTTTGATCTCGTGTGTGGCTGCCTTCCTATTTTCAAGGAAAGAC
GCCAAGGTAATTTTGACCCAGAGGAGCAATGATGTAGCCACCTCCTAACCTTCCCTTCTTTGAACCCCC
AGTTATGCCAGGATTTACTAGAGAGTGTCACTCAACAGCAGCGGCTCCTTCGGCTTAACTTGTGG
TTGGAGGAGAGAACTTTGTGGGGTGCCTTCTCTTAGCAGTGCTCAGAAGTGACTTGCCTGAGGGTG
GACCAGAAGAAAGGAAAGGTCCCCTCTTGCTGTTGGCTGCACATCAGGAAGGCTGTGATGGGAATGAA
GGTGAAAACCTTGGAGATTTCACTTCAGTCATTGCTTCTGCCTGCAAGATCATCCTTTAAAAGTAGAGA
AGCTGCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAAGGAAATGGATGCAAGCAGC
TCCGGGGGCCCCAAACGCATGCTTCTCTGTGTTCTAGCCACGGGAAGCCCTTCCGTGGGGGCCCGGGCT
TTGAGGGATGCCACCGGTTCTGGACGCATGGCTAGTTTCTGAATGATGATGGTTGCCTGGGGGGCTGCT
TGCTTGGATTTCCCGGGTGGTGGTTTGTGCTGGTGTCTCTCTGATGTGCTATCTCTGCTGTACATGT
TGGCCTGCACCCCAAAGGTGACGAGGAGCAGCTGGCACTGCCCAGGGCCAAACAGCCCCACGGGGAAG
GAGGGGTACCAGGCCGTCTTCAGGAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCG
GCAGATCGCACAGCTCAAGGAGGAGCTGCAGGAGAGGAGCTGAGCAGTTCAGGAATTGGGCAGTACCAAG
CCAGCGATGCTGCTGGCCTGGGTCTGGACAGGAGCCCGCAGAGAAACCCAGGCCACCTCTGGCC
TTCTTGCACTCGCAGGTGGAACAAGGCAGAGGTGAATGCTGGCGTCAAGCTGGCCACAGAGTATGCAGC
AGTGCTTTTCGATAGCTTTACTCTACAGAAGGTGTACCAGCTGGAGACTGGCCTTACCCGCCACCCCG
AGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAAGCCATTGAATCAGCCTTGGAGACC
CTGAACAATCCTGCGAGAAACAGGCCCAATCACCGTCTTACACCGCCTCTGATTTCATAGAAGGGAT
CTACCGAACAGAAAGGACAAGGGACATTGTATGAGCTCACCTTCAAAGGGGACCAACAAACGAAT
TCAAACGGCTCATCTTATTTGCACCATTAGCCCCATCATGAAAGTGAAAAATGAAAAGCTCAACATG
GCCAACACGCTTATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCCGGCAGTTTCATGCA
GAATTTACGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGGAAAG
AAGAAATAAATGAAGTCAAAGGAATACTTGAAAACACTTCCAAAGCTGCCAACTTCAGGAACCTTTACC
TTCACTCAGCTGAATGGAGAATTTCTCGGGGAAAGGGACATGTGATGTGGAGCCCGCTTCTGGAAGGG
AAGCAACGCTCCTTCTCTTTTCTGTGATGTGGACATCTACTCATCTGAAATTCCTCAATACGTGTA
GGCTGAATACACAGCCAGGGAAGAAGGTATTTTATCCAGTTCTTTTCAGTCAGTACAATCCTGGCATA
ATATACGGCCACCATGATGCAGTCCCTCCCTTGAACAGCAGCTGGTCATAAAGAAGGAAACTGGATT
TTGGAGAGACTTTTGGATTGGGATGACGTGTGATGATCGGTACAGCTTCATCAATATAGGTGGGTTTG
ATCTGGACATCAAAGGCTGGGGCGGAGGAGATGTGACCTTTATCGAAGTATCTCCACAGCAACCTC
ATAGTGGTACGGACGCCTGTGCGAGGACTCTCCACCTCTGGCATGAGAAGCGCTGCATGCAGCAGCT
GACCCCCGAGCAGTACAAGATGTGCATGCAGTCCAAGGCCATGAACGAGGCATCCACGGCCAGCTGG
GCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTTCGCAAAACAGAAACAGAAGACAAGTAGCAA
AAAACATGA~~AA~~ACTCCCAGAGAAGGATTTGTGGGAGACATTTTTCTTTTCTTTTGCAATTACTGAAAGTG
GCTGCAACAGAGAAAAGACTTCCATAAAGGACGACAAAAGAAATGGACTGATGGGTACAGAGATGAGAA
AGCCTCCGATTTCTCTCTGTGGGCTTTTACAACAGAAATCAAATCTCCGCTTTTGCCTGCAAAAGT
AACCCAGTTGCAACCCTGTGAAGTGTCTGACAAAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTG
TGGAGGTTTTGATGGTGTTTACAATACACTGAGACCTGTTGTTTTGTGTGCTCATTGAAATATTCATG
ATTTAAGAGCAGTTTTGTAAAAAATTCATTAGCATGAAAGGCCAAGCATATTTCTCCTCATATGAATGA
GCCTATCAGCAGGGCTCTAGTTTTCTAGGAATGCTAAAAATCAGAAGGCAGGAGGAGATAGGCTTA
TTATGATACTAGTGAGTACATTAAGTAAAAATAAATGGACCAGAAAAGAAAAGAAACATAAATATCG
TGTCAATTTTTCCCAAGATTAAACAAAAATAATCTGCTTATCTTTTTTGGTTGTCCTTTTAACTGTCT
CCGTTTTTTTTCTTTTATTTAAAAATGCACTTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTA
CCACTTTTGCAAGCCTTACAAGAGAGCACAAGTTGGCCTACATTTTTTATATTTTTTAAGAAGATACCTT
GAGATGCATTTATGAGAACTTTAGTTCAAAGCATCAAATGTAGGCCATATCCAAGGACATGCCAAATG
CTGATTTCTGTGAGGCATGAATGTGAGGCATGAGACATAGGGAAGGAATGGTTTTGTACTAATACAGA
CGTACAGATACTTTCTCTGAAGAGTATTTTCTGAAGAGGAGCAACTGAACTGAGGAGGAAAAGAAAATG
ACACTTTCTGCTTTACAGAAAAGGAAACTCATTGAGACTGGTGATATCGTGATGTACCTAAAAGTCAG
AAACCAATATTTCTCCTCAGAAAGTAGGGACCGCTTCTTACCTGTTTAAATAAACCAAAGTATACCGT
GTGAACCAACAATCTCTTTTCAAACAGGGTGCTCCTCTGGCTTCTGGCTTCCATAAGAAAGAAATG
GAGAAAATATATATATATATATATATATATATTTGTGAAGATCAATCCATCTGCCAGAACTAGTGGGATG
GAAGTTTTTGTACATGTTATCCACCCAGGCCAGGTGGAAGTAACCTGAATTATTTTTTAAATTAAGC
AGTTCTACTCAATCACAAGATGCTTCTGAAAATTGCATTTTATTACCATTTCAAACATTTTTTTTAAA
AATAAATACAGTTAACATAGAGTGGTTTTCTTCAATCATGTGAAAATTATTAGCCAGCACCAGATGCAT
GAGCTAATATCTCTTTGAGTCTTGTCTCTGTTTGTCTCAGTAAACTCATTGTTTAAAAAGCTTCAA
GAACATTAAGCTGTTGGTGTTTAAAAAATGCATGTATGATTTGTACTGGTAGTTTATGAAATTT
AATTAACACAGGCCATGAATGGAAGGTGGTATGCAAGCTAATAAATAATGATTTTGTGGATATGA

FIGURE 276

MMVRRGLLAWISRVVLLVLLCCAISVLYMLACTPKGDEEQLALPRANSPTGKEGYQAVLQ
EWEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADLLAFL
HSQVDKAEVNAGVKLATEYAAVPFDSFTLQKVYQLETGLTRHPEEKPVKDKRDELVEAIES
ALETLNNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLILFRPFSP
MKVKNEKLNMAN TLINVI VPLAKRVDKFRQFMQNFREMCIEQDGRVHLTVVYFGKEEINEVK
GILENTSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVDIYFTSEFLNTR
LNTQPGKKVFYPVLFSQYNPGIIYGHHDVPPLEQQLVIKKETGFWRDFGFGMTCQYRSDFI
NIGGFDLDIKGWGGEDVHLYRKYLHSNLI VVRTPVRGLFHLWHEKRCMDELTPEQYKMCMQS
KAMNEASHGQLGMLVFRHEIEAHLRKQKQKTSSKKT

FIGURE 277

GAAAGAATGTTGTGGCTGCTCTTTTTCTGGTGACTGCCATTCATGCTGAACTCTGTCAACC
AGGTGCAGAAAATGCTTTTAAAGTGAGACTTAGTATCAGAACAGCTCTGGGAGATAAAGCAT
ATGCCTGGGATACCAATGAAGAATACCTCTTCAAAGCGATGGTAGCTTTCTCCATGAGAAAA
GTTCCCAACAGAGAAGCAACAGAAATTTCCCATGTCCTACTTTGCAATGTAACCCAGAGGGT
ATCATTCTGGTTTGTGGTTACAGACCCTTCAAAAAATCACACCCTTCCTGCTGTTGAGGTGC
AATCAGCCATAAGAATGAACAAGAACCGGATCAACAATGCCTTCTTTCTAAATGACCAAAC
CTGGAATTTTTAAAAATCCCTTCCACACTTGCAACCCCATGGACCCATCTGTGCCCATCTG
GATTATTATATTTGGTGTGATATTTTGCATCATCATAGTTGCAATTGCACTACTGATTTTAT
CAGGGATCTGGCAACGTAGAAGAAAGAACAAAGAACCATCTGAAGTGGATGACGCTGAAGAT
AAGTGTGAAAACATGATCACAATTGAAAATGGCATCCCCCTCTGATCCCCCTGGACATGAAGGG
GGGCATATTAATGATGCCTTCATGACAGAGGATGAGAGGCTCACCCCTCTCTGAAGGGCTGT
TGTTCTGCTTCCTCAAGAAATTAAACATTTGTTTCTGTGTGACTGCTGAGCATCCTGAAATA
CCAAGAGCAGATCATATATTTTGTTTCACCATTCCTCTTTTGTAAATAAATTTTGAATGTGCT
TGAAAGTGAAAAGCAATCAATTATACCCACCAACACCACTGAAATCATAAGCTATTCACGAC
TCAAAATATTCTAAATATTTTTCTGACAGTATAGTGTATAAATGTGGTCATGTGGTATTTG
TAGTTATTGATTTAAGCATTTTTAGAAATAAGATCAGGCATATGTATATATTTTCACACTTC
AAAGACCTAAGGAAAAATAAATTTTCCAGTGGAGAATACATATAATATGGTGTAGAAATCAT
TGAAAATGGATCCTTTTTGACGATCACTTATATCACTCTGTATATGACTAAGTAAACAAAAG
TGAGAAGTAATTATTGTAAATGGATGGATAAAAATGGAATTACTCATATACAGGGTGGAATT
TTATCCTGTTATCACACCAACAGTTGATTATATATTTTCTGAATATCAGCCCCTAATAGGAC
AATTCTATTTGTTGACCATTTCTACAATTTGTAAAAGTCCAATCTGTGCTAACTTAATAAAG
TAATAATCATCTCTTTTTAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 278

MLWLLFFLVTAIHAELCQPGAENAFKVRLSIRTALGDKAYAWDTNEEYLFKAMVAFSMRKVP
NREATEISHVLLCNVTQRVSFWFVVTDP SKNHTLP AVEVQSAIRMNKNRINNAFFLNDQ TLE
FLKIPSTLAPPMDPSVPIWIIIFGVIFCIIIVAIALLLSGIWQRRRKNKEPSEVDDAEDKC
ENMITIENGIPSDPLDMKGGILMMP S

FIGURE 279

AACTCAAACCTCCTCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCAGG
GTGTTGGAGCCCTCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTCATGT
ATGGCAAGAGCTCTACTCGTGCGGTGCTTCTTCTCCTTGGCATAACAGCTCACAGCTCTTTGG
CCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTGTCTGGAGGCTGTTAATGGGACAGATGC
TCGGTTAAATGCACTTTCTCCAGCTTTGCCCCGTGTGGGTGATGCTCTAACAGTGACCTGGA
ATTTTCGTCTCTAGACGGGGACCTGAGCAGTTTGTATTCTACTACCACATAGATCCCTTC
CAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAATCCTGAGCGGTACGA
TGCTCCATCCTTCTCTGGAACTGCAGTTCGACGACAATGGGACATACACCTGCCAGGTGA
AGAACCCACCTGATGTTGATGGGGTGATAGGGGAGATCCGGCTCAGCGTCGTGCACACTGTA
CGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCATTGGCTCTGCCTGTGCACTGATGATCAT
AATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAAAAGCGATGGGCCGAAAGAGCTC
ATAAAGTGGTGGAGATAAAATCAAAGAAGAGGAAAGGCTCAACCAAGAGAAAAAGGTCTCT
GTTTATTTAGAAGACACAGACTAAACAATTTTAGATGGAAGCTGAGATGATTTCCAAGAACAA
GAACCCTAGTATTTCTTGAAGTTAATGGAACTTTTCTTTGGCTTTTCCAGTTGTGACCCGT
TTTCCAACCAGTCTGCAGCATATTAGATTCTAGACAAGCAACACCCCTCTGGAGCCAGCAC
AGTGCTCCTCCATATCACCAGTCATACACAGCCTCATTATTAAGGTCTTATTTAATTTCAGA
GTGTAAATTTTTTCAAGTGCTCATTAGGTTTTATAACAAGAAGCTACATTTTTTGCCCTTAA
GACACTACTTACAGTGTTATGACTTGTATACACATATATTGGTATCAAAGGGGATAAAAGCC
AATTTGTCTGTTACATTTCTTTTACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTA
ATGTGTTTACTCTCTTTCCCTTCCCACATTCTCAATTAAAAGGTGAGCTAAGCCTCCTCGGTG
TTTCTGATTAAACAGTAAATCCTAAATTCAAACCTGTTAAATGACATTTTTATTTTTATGTCTC
TCCTTAACTATGAGACACATCTTGTTTTACTGAATTTCTTTCAATATTCCAGGTGATAGATT
TTTGTCG

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FIGURE 280

MYGKSSTRAVLLLLGIQLTALWPAAVEIYTSRVLEAVNGTDARLKCTFSSFAPVGDALTVT
WNFRPLDGGPEQFVFYYHIDPFQPMSEGRFKDRVSWDGNPERYDASILLWKLQFDDNGTYTCQ
VKNPPDVDGVIGEIRLSVVHTVRFSEIHFLALAIGSACALMI I I V I V V V L F Q H Y R K K R W A E R
AHKVVEIKSKEEERLNQEKKVSVYLETD

FIGURE 281

GCATTTTTGTCTGTGCTCCCTGATCTTCAGGTCACCACCATGAAGTTCTTAGCAGTCCTGGT
ACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTCCAGCTG
ACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCACTGCTGCT
GCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACCACTGCTCG
TAAAGACATTCCAGTTTTACCCAAATGGGTTGGGGATCTCCCGAATGGTAGAGTGTGTCCCT
GAGATGGAATCAGCTTGAGTCTTCTGCAATTGGTCACAACCTATTCATGCTTCCTGTGATTTC
ATCCAACCTACTTACCTTGCCTACGATATCCCCTTTATCTCTAATCAGTTTATTTTCTTTCAA
ATAAAAAATAACTATGAGCAACATAAAAAAAAAAAAAA

FIGURE 282

MKFLAVLVLLGVSI FLVSAQNPTTAAPADTYPATGPADDEAPDAETTAAATTATTAAPTTAT
TAASTTARKDIPVLPKWVGDL PNGRVCP

FIGURE 283

GGACTCTGAAGGTCCCAAGCAGCTGCTGAGGCCCCCAAGGAAGTGGTTCCAACCTTGGACCC
CTAGGGGTCTGGATTTGCTGGTTAACAAGATAACCTGAGGGCAGGACCCCATAGGGGAATGC
TACCTCCTGCCCTTCCACCTGCCCTGGTGTTACGGTGGCCTGGTCCCTCCTTGCCGAGAGA
GTGTCCTGGGTGAGGGACGCAGAGGACGCTCACAGACTCCAGCCCTTTGTTACCGAGAGGAC
ACTTGGCAAGGTCCAGCGATGGTCCGGAGTCCACACACAGACTGGCGGCAGGGCAGGAGGGG
GACAGTTCTGTTGTGCTTGGTTGGACAGTAAGAGGGTCTTGGCCAGTCCAGGGTGGGGGGCG
GCAAACCTCCATAAAGAACCAGAGGGTCTGGGCCCCGGCCACAGAGTCATCTGCCAGCTCCT
CTGCTGCTGGCCAGTGGGAGTGGCACGAGGTGGGGCTTTGTGCCAGTAAACACAGGCTGG
ATTTGCCTGCGGGCCATGGTCCCTGTCTAGGGCAGCAATTCTCAACCTTCTTGCTCTCAGGA
CCCCAAAGAGCTTTCATTGTATCTATTGATTTTTACCACATTAGCAATTAAACTGAGAAAT
GGGCCGGGCACGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGTGGAT
CACCTGAGATCAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCTTGTCTACTAAAAA
TACAAAAAATTAGCCAGGCACAGTGGTGTGCACTGGTAGTCCCAGTTACTCGGGAGGCTGAG
GCAGGAAAATCGCTTGAACCCAGGAGGCGGACGTTGCGGTGAGCCGAGATCGCGCCGCTGAT
TCCAGCCTGGGCGACAAGAGTGAGACTCCATCTCACACA

FIGURE 284

MLPPALPPALVFTVAWSLLAERVSWVRDAEDAHRLQPFVTERTLGKVQRWSGVHTQTGGRAG
GGQFCCAWLDSKRVLASPGWGAANSIKNQRVWAPATESSAQLLCCWPVGVARGGALCQ

FIGURE 285

GTCATGCCAGTGCCTGCTCTGTGCCTGCTCTGGGCCCTGGCAATGGTGACCCGGCCTGCCTCA
GCGGCCCCCATGGGCGGCCCAGAACTGGCACAGCATGAGGAGCTGACCCTGCTCTTCCATGG
GACCCTGCAGCTGGGCCAGGCCCTCAACGGTGTGTACAGGACCACGGAGGGACGGCTGACAA
AGGCCAGGAACAGCCTGGGTCTCTATGGCCGCACAATAGAACTCCTGGGGCAGGAGGTGAGC
CGGGGCCGGGATGCAGCCCAGGAACCTTCGGGCAAGCCTGTTGGAGACTCAGATGGAGGAGGA
TATTCTGCAGCTGCAGGCAGAGGCCACAGCTGAGGTGCTGGGGGAGGTGGCCCAGGCACAGA
AGGTGCTACGGGACAGCGTGCAGCGGCTAGAAGTCCAGCTGAGGAGCGCCTGGCTGGGCCCT
GCCTACCGAGAATTTGAGGTCTTAAAGGCTCACGCTGACAAGCAGAGCCACATCCTATGGGC
CCTCACAGGCCACGTGCAGCGGCAGAGGCGGGAGATGGTGGCACAGCAGCATCGGCTGCGAC
AGATCCAGGAGAGACTCCACACAGCGGCGCTCCCAGCCTTGAATCTGCCTGGATGGAAGTGA
GACCAATCATGCTGCAAGGAACACTTCCACGCCCCGTGAGGCCCTGTGCAGGGAGGAGCTG
CCTGTTCACTGGGATCAGCCAGGGCGCCGGGCCCCACTTCTGAGCACAGAGCAGAGACAGAC
GCAGGCGGGGACAAAGGCAGAGGATGTAGCCCCATTGGGGAGGGGTGGAGGAAGGACATGTA
CCCTTTCATGCCTACACACCCCTCATTAAGCAGAGTCGTGGCATTTCAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 286

MPVPALCLLWALAMVTRPASAAPMGGPELAQHEELTLLFHGTLQLGQALNGVYRTTEGRLTK
ARNSLGlyGRTIELLGQEVSRGRDAAQELRASLLETQMEEDILQLQAEATAEVLGEVAQAQK
VLRDSVQRLEVQLRSAWLGPAYREFEVLKAHADKQSHILWALTGHVQRQRREMVAQQHRLRQ
IQERLHTAALPA

FIGURE 287

GGCAACATGGCTCAGCAGGCTTGCCCCAGAGCCATGGCAAAGAATGGACTTGTAATTTGCAT
CCTGGTGATCACCTTACTCCTGGACCAGACCACCAGCCACACATCCAGATTAAAAGCCAGGA
AGCACAGCAAACGTCGAGTGAGAGACAAGGATGGAGATCTGAAGACTCAAATTGAAAAGCTC
TGGACAGAAGTCAATGCCTTGAAGGAAATTCAAGCCCTGCAGACAGTCTGTCTCCGAGGCAC
TAAAGTTCACAAGAAATGCTACCTTGCTTCAGAAGGTTTGAAGCATTTCCATGAGGCCAATG
AAGACTGCATTTCCAAAGGAGGAATCCTGGTTATCCCCAGGAACTCCGACGAAATCAACGCC
CTCCAAGACTATGGTAAAAGGAGCCTGCCAGGTGTCAATGACTTTTGGCTGGGCATCAATGA
CATGGTCACGGAAGGCAAGTTTGTGTGACGTCAACGGAATCGCTATCTCCTTCCTCAACTGGG
ACCGTGACAGCCTAACGGTGGCAAGCGAGAAAACTGTGTCTGTCTCCCAATCAGCTCAG
GGCAAGTGGAGTGATGAGGCCTGTGCGAGCAGCAAGAGATACATATGCGAGTTCACCATCCC
TAAATAGGTCTTTCTCCAATGTGTCTCCAAGCAAGATTCATCATAACTTATAGGTTTCATGA
TCTCTAAGATCAAGTAAAAATCATAATTTTTACTTATTAAAAAATTGCAACACAAGATCAAT
GTCCATAGCAATATGATAGCATCAGCCAATTTTGCTAACACATTTCTTTGGGATTTTGCCCT
TCCTGGGGTATAGGGGATCAGAAATATTGATCCATGTGCACGCAGATAAAATGGCTTCTGTCT
AAACAGACTAAAATCTTTCTCTCTAGTCTTTCTCACTTGTACAAACCCAGTTTGTTTTCAA
AAATCACAGTAGCAATGCAACTCATCACTCTAGAAAAGCAAGCTTAGGCTACCTGAAAGATT
TTCCCTTGGAAGTTTAGCGTATGTTTGACTAACAAAAATTCCCTACATCAGAGACTCTAGGT
GCTATATAATCCAAAACTTTTCAGCCTGTTGCTCATTCTGTCCCATGCTGGCAATAATACC
TTGTCAGCCCATTACCCTTATTTTGAATTGCTCCATCTCCTGGTGGGACTTGTATCTTGTCT
GCCATATCAGAACACAAACCCCTGAAGAGGTTCTGATTTGATTTTTTTTTTTTCTTCATGCC
TACCCTTTTTTTGGAAGTTTCCAGCCGCAATTTGAAATGAAATGACAAGGTGTATATTTGAT
CAATTTTCATTCCCACCATTCGATTACAACCTCTAACTTAAATGGGTAACCCTAAGGCATAT
CAAAGAAGCAGATTGCATGATAAACGGAAATAGAAAAAAGAACCTACATTTATTTTGCTTT
AGCATCCTTACTCTCACCTTTTATGAGATTGAGAGTGGACTTACATTTCCCTTTTTTACATTT
TCGTATATTTATTTTTTTTAGCCATCATTATATGTTTAAGTCTATTATGGGCAACCAATCTT
TGGAAGCTGAAAATGAATTTAAAGAATGCTATCTTGGAATTTGCATACGTCTGTGCAATT
TTTTATTCTGCCTAGTGCTATTCTGCTTGTTTAACTAGATTGTACAAAATAACTTCATTGCT
TAATATCAAATTACAAAGTTTAGACTTGGAGGGGAAATGGGCTTTTTTAGAAGCAAACAATTTT
AAATATATTTTGTTCCTTCAAATAAATAGTGTTTAAACATTGAATGTGTTTTGTGAACAATAT
CCCACTTTGCAAACCTTAACTACACATGCTTGGAATTAAGTTTTAGCTGTTTTTCATTGCTCA
ATAATAAAGCCTGAATTCTGATCAATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 288

MAQQACPRAMAKNGLVICILVITLLLDQTTSHTSRLKARKHSKRRVRDKDGD LKTQIEKLWT
EVNALKEIQALQTVCLRGTKVHKKCYLASEGLKHFHEANEDCISKGGILVIPRNSDEINALQ
DYGKRSLPGVNDFWLGINDMVTEGKFVDVNGIAISFLNWDRAQPNGGKRENCVLFSSAQGK
WSDEACRSSKRYICEFTIPK

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FIGURE 289

GCGAGGACCGGGTATAAGAAGCCTCGTGCCCTTGCCCGGGCAGCCGCAGGTTCCCCGCGCGC
CCCCAGCCCCCGCGCCATGAAGCTCGCCGCCCTCCTGGGGCTCTGCGTGCGCCCTGTCCTGCA
GCTCCGCTGCTGCTTTCTTAGTGGGCTCGGCCAAGCCTGTGGCCCAGCCTGTCGCTGCGCTG
GAGTCGGCGGCGGAGGCCGGGGCCGGGACCCTGGCCAACCCCTCGGCACCCTCAACCCGCT
GAAGCTCCTGCTGAGCAGCCTGGGCATCCCCGTGAACCACCTCATAGAGGGCTCCCAGAAGT
GTGTGGCTGAGCTGGGTCCCCAGGCCGTGGGGGCCGTGAAGGCCCTGAAGGCCCTGCTGGGG
GCCCTGACAGTGTTTGGCTTGAGCCGAGACTGGAGCATCTACACCTGAGGACAAGACGCTGCC
CACCCGCGAGGGCTGAAAACCCCGCCGCGGGGAGGACCGTCCATCCCCTTCCCCGGCCCCCT
CTCAATAAACGTGGTTAAGAGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAA

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FIGURE 290

MKLAALLGLCVALSCSSAAFLVGSAPVAPVAALESAAEAGAGTLANPLGTLNPLKLLLS
SLGIPVNHLEGSQKCVNELGPQAVGAVKALKALLGALT VFG

FIGURE 291

TGAAGGACTTTTCCAGGACCCAAGGCCACACACTGGAAGTCTTGCAGCTGAAGGGAGGCACT
CCTTGGCCTCCGCAGCCGATCACATGAAGGTGGTGCCAAGTCTCCTGCTCTCCGTCCTCCTG
GCACAGGTGTGGCTGGTACCCGGCTTGGCCCCCAGTCCCTCAGTCGCCAGAGACCCCAGCCCC
TCAGAACCAGACCAGCAGGGTAGTGCAGGCTCCCAGGGAGGAAGAGGAAGATGAGCAGGAGG
CCAGCGAGGAGAAGGCCGGTGAGGAAGAGAAAGCCTGGCTGATGGCCAGCAGGCAGCAGCTT
GCCAAGGAGACTTCAAACCTTCGGATTTCAGCCTGCTGCGAAAGATCTCCATGAGGCACGATGG
CAACATGGTCTTCTCTCCATTTGGCATGTCCTTGGCCATGACAGGCTTGATGCTGGGGGCCA
CAGGGCCGACTGAAACCCAGATCAAGAGAGGGGCTCCACTTGCAGGCCCTGAAGCCCACCAAG
CCCGGGCTCCTGCCTTCCCTCTTTAAGGGACTCAGAGAGACCTCTCCCGCAACCTGGAAGT
GGGCCTCTCACAGGGGAGTTTTGCCTTCATCCACAAGGATTTTGATGTCAAAGAGACTTTCT
TCAATTTATCCAAGAGGTATTTTGATACAGAGTGCCTGCTATGAATTTTCGCAATGCCTCA
CAGGCCAAAAGGCTCATGAATCATTACATTAACAAAAGAGACTCGGGGGAAAATTCCCAAAC
GTTTGATGAGATTAATCCTGAAACCAAATTAATTCTTGTGGATTACATCTTGTTCAAAGGGA
AATGGTTGACCCCATTTGACCCTGTCTTCACCGAAGTCGACACTTTCCACCTGGACAAGTAC
AAGACCATTAAGGTGCCCATGATGTACGGTGCAGGCAAGTTTGCTCCACCTTTGACAAGAA
TTTTCGTTGTTCATGTCCTCAAACCTGCCCTACCAAGGAAATGCCACCATGCTGGTGGTCTCTCA
TGGAGAAAATGGGTGACCACCTCGCCCTTGAAGACTACCTGACCACAGACTTGGTGGAGACA
TGGCTCAGAAACATGAAAACCAGAAACATGGAAGTTTTCTTTCCGAAGTTCAAGCTAGATCA
GAAGTATGAGATGCATGAGCTGCTTAGGCAGATGGGAATCAGAAGAATCTTCTCACCTTTG
CTGACCTTAGTGAACCTCTCAGCTACTGGAAGAAATCTCCAAGTATCCAGGGTTTTACGAAGA
ACAGTGATTGAAGTTGATGAAAGGGGCACTGAGGCAGTGGCAGGAATCTTGTCAGAAATTAC
TGCTTATTCCATGCCTCCTGTCATCAAAGTGGACCGGCCATTTCAATTCATGATCTATGAAG
AAACCTCTGGAATGCTTCTGTTTCTGGGCAGGGTGGTGAATCCGACTCTCCTATAAATTCAGG
ACATGCATAAGCACTTCGTGCTGTAGTAGATGCTGAATCTGAGGTATCAAACACACACAGGA
TACCAGCAATGGATGGCAGGGGAGAGTGTTCCTTTTGTTCCTTAAGTAGTTTAGGGTGTTC
AAATAAATACAGTAGTCCCCACTTATCTGAGGGGGATACATTCAAAGACCCCCAGCAGATGC
CTGAAACGGTGGACAGTGCTGAACCTTATATATATTTTTTCTACACATACATACCTATGAT
AAAGTTTAATTTATAAATTAGGCACAGTAAGAGATTAACAATAATAACAACATTAAGTAAAA
TGAGTTACTTGAACGCAAGCACTGCAATACCATAACAGTCAAACCTGATTATAGAGAAGGCTA
CTAAGTGACTCATGGGCGAGGAGCATAGACAGTGTGGAGACATTGGGCAAGGGGAGAATTCA
CATCCTGGGTGGGACAGAGCAGGACGATGCAAGATTCCATCCCACTACTCAGAATGGCATGC
TGCTTAAGACTTTTAGATTGTTTATTTCTGGAATTTTTCATTTAATGTTTTTGGACCATGGT
TGACCATGGTTAACTGAGACTGCAGAAAGCAAACCATGGATAAGGGAGGACTACTACAAAA
GCATTAAATTGATACATATTTTTTAAAAA

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FIGURE 292

MKVVP S L L L S V L L A Q V W L V P G L A P S P Q S P E T P A P Q N Q T S R V V Q A P R E E E E D E Q E A S E E K A G E
E E K A W L M A S R Q Q L A K E T S N F G F S L L R K I S M R H D G N M V F S P F G M S L A M T G L M L G A T G P T E T Q I
K R G L H L Q A L K P T K P G L L P S L F K G L R E T L S R N L E L G L S Q G S F A F I H K D F D V K E T F F N L S K R Y F
D T E C V P M N F R N A S Q A K R L M N H Y I N K E T R G K I P K L F D E I N P E T K L I L V D Y I L F K G K W L T P F D P
V F T E V D T F H L D K Y K T I K V P M M Y G A G K F A S T F D K N F R C H V L K L P Y Q G N A T M L V V L M E K M G D H L
A L E D Y L T T D L V E T W L R N M K T R N M E V F F P K F K L D Q K Y E M H E L L R Q M G I R R I F S P F A D L S E L S A
T G R N L Q V S R V L R R T V I E V D E R G T E A V A G I L S E I T A Y S M P P V I K V D R P F H F M I Y E E T S G M L L F
L G R V V N P T L L

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FIGURE 293

CTGGGATCAGCCACTGCAGCTCCCTGAGCACTCTCTACAGAGACGCGGACCCCAGACATGAG
GAGGCTCCTCCTGGTCACCAGCCTGGTGGTTGTGCTGCTGTGGGAGGCAGGTGCAGTCCCAG
CACCCAAGGTCCCTATCAAGATGCAAGTCAAACACTGGCCCTCAGAGCAGGACCCAGAGAAG
GCCTGGGGCGCCCGTGTGGTGGAGCCTCCGGAGAAGGACGACCAGCTGGTGGTGTGTTCCC
TGTCAGAAGCCGAAACTCTTGACCACCGAGGAGAAGCCACGAGGTCAGGGCAGGGGCCCCA
TCCTTCCAGGCACCAAGGCCTGGATGGAGACCGAGGACACCCTGGGCCGTGTCCTGAGTCCC
GAGCCCGACCATGACAGCCTGTACCACCCTCCGCCTGAGGAGGACCAGGGCGAGGAGAGGCC
CCGGTTGTGGGTGATGCCAAATCACCAGGTGCTCCTGGGACCGGAGGAAGACCAAGACCACA
TCTACCACCCCCAGTAGGGCTCCAGGGGCCATCACTGCCCCCGCCCTGTCCCAAGGCCCAGG
CTGTTGGGACTGGGACCCTCCCTACCCTGCCCCAGCTAGACAAATAAACCCAGCAGGCAAA
AAAAAAAAAAAAAAAAA

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FIGURE 294

MRRLLLVTSLVVLLWEAGAVPAPKVPIKMQVKHWPSEQDPEKAWGARVVEPPEKDDQLVVL
FPVQKPKLLTTEEKPRGQGRGPILPGTKAWMETEDTLGRVLSPEPDHDSLYHPPPEEDQGEE
RPRLWVMPNHQVLLGPEEDQDHIYHPQ

FIGURE 295

AGAAAGCTGCACTCTGTTGAGCTCCAGGGCGCAGTGGAGGGAGGGAGTGAAGGAGCTCTCTG
TACCCAAGGAAAGTGCAGCTGAGACTCAGACAAGATTACAATGAACCAACTCAGCTTCCTGC
TGTTTCTCATAGCGACCACCAGAGGATGGAGTACAGATGAGGCTAATACTTACTTCAAGGAA
TGGACCTGTTCTTCGTCTCCATCTCTGCCCAGAAGCTGCAAGGAAATCAAAGACGAATGTCC
TAGTGCAATTTGATGGCCTGTATTTTCTCCGCACTGAGAATGGTGTTATCTACCAGACCTTCT
GTGACATGACCTCTGGGGGTGGCGGCTGGACCCTGGTGGCCAGCGTGCAAGAGAATGACATG
CGTGGGAAGTGCACGGTGGGCGATCGCTGGTCCAGTCAGCAGGGCAGCAAAGCAGACTACCC
AGAGGGGGACGGCAACTGGGCCAACTACAACACCTTTGGATCTGCAGAGGCGGCCACGAGCG
ATGACTACAAGAACCTGGCTACTACGACATCCAGGCCAAGGACCTGGGCATCTGGCACGTG
CCCAATAAGTCCCCCATGCAGCACTGGAGAAACAGCTCCCTGCTGAGGTACCGCACGGACAC
TGGCTTCCTCCAGACACTGGGACATAATCTGTTTGGCATCTACCAGAAATATCCAGTGAAAT
ATGGAGAAGGAAAGTGTGGACTGACAACGGCCCCGGTGATCCCTGTGGTCTATGATTTTGGC
GACGCCCAGAAAACAGCATCTTATTACTCACCTATGGCCAGCGGAATTCAGTGCGGGATT
TGTTCAAGTTCAGGGTATTTAATAACGAGAGAGCAGCCAACGCCTTGTGTGCTGGAATGAGGG
TCACCGGATGTAACACTGAGCATCACTGCATTGGTGGAGGAGGATACTTTCCAGAGGCCAGT
CCCCAGCAGTGTGGAGATTTTCTGGTTTTGATTGGAGTGGATATGGAACTCATGTTGGTTA
CAGCAGCAGCCGTGAGATAACTGAGGCAGCTGTGCTTCTATTCTATCGTTGAGAGTTTTGTG
GGAGGGAACCCAGACCTCTCCTCCCAACCATGAGATCCCAAGGATGGAGAACAACCTTACCCA
GTAGCTAGAATGTTAATGGCAGAAGAGAAAACAATAAATCATATTGACTCAAGAAAAAAA

FIGURE 296

MNQLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRTEN
GVIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRWSSQQGSKADYPEGDGNWANYNTFG
SAEAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLLRYRTDTGFLQTLGHNLFGI
YQKYPVKYGEKGCWTDNGPVI PVVYDFGDAQKTASYSPYGQREFTAGFVQFRVFNNERAAN
ALCAGMRVTGCNTEHHCIGGGGYFPEASPQQCGDFSGFDWSGYGTHVGYSSSREITEAAVLLFYR

FIGURE 297

GCGGAGCCGGCGCCGGCTGCGCAGAGGAGCCGCTCTCGCCGCCGCCACCTCGGCTGGGAGCC
CACGAGGCTGCCGCATCCTGCCCTCGGAACAATGGGACTCGGCGCGCGAGGTGCTTGGGCCG
CGCTGCTCCTGGGGACGCTGCAGGTGCTAGCGCTGCTGGGGGCCGCCCATGAAAGCGCAGCC
ATGGCGGCATCTGCAAACATAGAGAATTCTGGGCTTCCACACAACTCCAGTGCTAACTCAAC
AGAGACTCTCCAACATGTGCCTTCTGACCATACAAATGAACTTCCAACAGTACTGTGAAAC
CACCAACTTCAGTTGCCTCAGACTCCAGTAATACAACGGTCACCACCATGAAACCTACAGCG
GCATCTAATAACAACAACACCAGGGATGGTCTCAACAAATATGACTTCTACCACCTTAAAGTC
TACACCCAAAACAACAAGTGTTTCACAGAACACATCTCAGATATCAACATCCACAATGACCG
TAACCCACAATAGTTTCAGTGACATCTGCTGCTTCATCAGTAACAATCACAACAACCTATGCAT
TCTGAAGCAAAGAAAGGATCAAAATTTGATACTGGGAGCTTTGTTGGTGGTATTGTATTAAC
GCTGGGAGTTTTATCTATTCTTTACATTGGATGCAAATGTATTACTCAAGAAGAGGCATTCT
GGTATCGAACCATAGATGAACATGATGCCATCATTTAAGGAAATCCATGGACCAAGGATGGA
ATACAGATTGATGCTGCCCTATCAATTAATTTTGGTTTATTAATAGTTTAAAACAATATTCT
CTTTTTGAAAATAGTATAAACAGGCCATGCATATAATGTACAGTGTATTACGTAAATATGTA
AAGATTCTTCAAGGTAACAAGGGTTTGGGTTTTGAAATAAACATCTGGATCTTATAGACCGT
TCATACAATGGTTTTAGCAAGTTCATAGTAAGACAAACAAGTCCTATCTTTTTTTTTTGGCT
GGGGTGGGGGCATTGGTCACATATGACCAGTAATTGAAAGACGTCATCACTGAAAGACAGAA
TGCCATCTGGGCATACAAATAAGAAGTTTGTACAGCACTCAGGATTTTGGGTATCTTTTGT
AGCTCACATAAAGAACTTCAGTGCTTTTCAGAGCTGGATATATCTTAATTACTAATGCCACA
CAGAAATTATACAATCAAACCTAGATCTGAAGCATAATTTAAGAAAAACATCAACATTTTTTG
TGCTTTAAACTGTAGTAGTTGGTCTAGAAACAAAATACTCC

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FIGURE 298

MGLGARGAWAALLLGTQLQVLALLGAAHESAAMAASANIENSGLPHNSSANSTETLQHVPDH
TNETSNSTVKPPTSVASDSSNTTVTTMKPTAASNTTTPGMVSTNMTSTTLKSTPKTTSVSQN
TSQISTSTMTVTHNSSVTSAASSVTITTTMHSEAKKGSKFDTGSFVGGIVLTGLVLSILYIG
CKMYYSRRGIRYRTIDEHDAII

FIGURE 299

CAGCCGGGTCCCAAGCCTGTGCCTGAGCCTGAGCCTGAGCCTGAGCCCCAGCCGGGAGCCGG
TCGCGGGGGCTCCGGGCTGTGGGACCGCTGGGCCCCAGCGATGGCGACCCTGTGGGGAGGC
CTTCTTCGGCTTGGCTCCTTGCTCAGCCTGTCGTGCCTGGCGCTTCCGTGCTGCTGCTGGC
GCAGCTGTCAGACGCCGCCAAGAATTTGAGGATGTCAGATGTAAATGTATCTGCCCTCCCT
ATAAAGAAAATTCTGGGCATATTTATAATAAGAACATATCTCAGAAAGATTGTGATTGCCTT
CATGTTGTGGAGCCCATGCCTGTGCGGGGGCCTGATGTAGAAGCATACTGTCTACGCTGTGA
ATGCAAATATGAAGAAAGAAGCTCTGTCACAATCAAGGTTACCATTATAATTTATCTCTCCA
TTTTGGGCCTTCTACTTCTGTACATGGTATATCTTACTCTGGTTGAGCCCATACTGAAGAGG
CGCCTCTTTGGACATGCACAGTTGATACAGAGTGATGATGATATTGGGGATCACCAGCCTTT
TGCAAATGCACACGATGTGCTAGCCCGCTCCCGCAGTCGAGCCAACGTGCTGAACAAGGTAG
AATATGCACAGCAGCGCTGGAAGCTTCAAGTCCAAGAGCAGCGAAAGTCTGTCTTTGACCGG
CATGTTGTCTCAGCTTAATTGGGAATTGAATTCAAGGTGACTAGAAAGAAACAGGCAGACAA
CTGGAAAGAACTGACTGGGTTTTGCTGGGTTTCATTTTAATACCTTGTTGATTTACCAACT
GTTGCTGGAAGATTCAAACTGGAAGCAAAAACCTTGCTTGATTTTTTTTTCTTGTTAACGTA
ATAATAGAGACATTTTTTAAAGCACACAGCTCAAAGTCAGCCAATAAGTCTTTTCCTATTTG
TGACTTTTACTAATAAAAAATAAATCTGCCTGTAAATTATCTTGAAGTCCTTTACCTGGAACA
AGCACTCTCTTTTTTACCACATAGTTTTTAACCTTGACTTTCAAGATAATTTTCAGGGTTTTTG
TTGTTGTTGTTTTTTGTTTGTGTTTGGTGGGAGAGGGGAGGGATGCCTGGGAAGTGTT
AACAACTTTTTTCAAGTCACTTTACTAAACAACTTTTGTAATAGACCTTACCTTCTATTT
TCGAGTTTCATTTATATTTTGCAGTG TAGCCAGCCTCATCAAAGAGCTGACTTACTCATTTG
ACTTTTGCAGTACTGTATTATCTGGGTATCTGCTGTGTCTGCACTTCATGGTAAACGGGAT
CTAAAATGCCTGGTGGCTTTTCACAAAAGCAGATTTTCTTCATGTACTGTGATGTCTGATG
CAATGCATCCTAGAACAACTGGCCATTTGCTAGTTTACTCTAAAGACTAAACATAGTCTTG
GTGTGTGTGGTCTTACTCATCTTCTAGTACCTTTAAGGACAAATCCTAAGGACTTGGA
TGCAATAAAGAAATTTTATTTTAAACCAAGCCTCCCTGGATTGATAATATATACACATTTG
TCAGCATTTCCGGTCGTGGTGAGAGGCAGCTGTTTGAGCTCCAATATGTGCAGCTTTGAACT
AGGGCTGGGGTTGTGGGTGCCTCTTCTGAAAGGTCTAACCATTATTGGATAACTGGCTTTTT
TCTTCCTATGTCCTCTTTGGAATGTAACAATAAAAATAATTTTGAAACATCAA

FIGURE 300

MATLWGGLRLGSLLSLSCLALSVLLLAQLSDAAKNFEDVRCKCICPPYKENS
GHYNNKIS
QKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIIYLSILG
LLLLLYMVYLT
LVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLA
RSRANVLNKVEYAQQRWKLQVQEQ
RKSVFDRHVLS

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FIGURE 301

GCACCTGCGACCACCGTGAGCAGTCATGGCGTACTCCACAGTGCAGAGAGTCGCTCTGGCTT
CTGGGCTTGTCTGGCTCTGTCTGCTGCTGCCCAAGGCCTTCCTGTCCCGCGGGAAGCGG
CAGGAGCCGCGCCGACACCTGAAGGAAAATTGGGCCGATTTCCACCTATGATGCATCATCA
CCAGGCACCCTCAGATGGCCAGACTCCTGGGGCTCGTTTCCAGAGGTCTCACCTTGCCGAGG
CATTTGCAAAGGCCAAAGGATCAGGTGGAGGTGCTGGAGGAGGAGGTAGTGGAAGAGGTCTG
ATGGGGCAGATTATTCCAATCTACGGTTTTGGGATTTTTTTATATATACTGTACATTCTATT
TAAGGTAAGTAGAATCATCCTAATCATATTACATCAATTGAAAATCTAATATGGCGATAAAAA
TCATTGTCTACATTAAAACTTCTTATAGTTCATAAAATTATTTCAAATCCATCATCTCTTTA
AATCCTGCCTCCTCTTCATGAGGTACTTAGGATAGCCATTATTTTCAGTTTCACATAAGAATG
TTTACTCAATGTTTAAGTGTTTTGCCCCAAAATTCACAATAACAAGGCAGAACTAGGACTT
GAACATGGATCTTTTGGTTCTTAATCCAGTGAGTGATACAATTCAATGCACTCCCCTGCCA

FIGURE 302

MAYSTVQRVALASGLVLALSLLLPKAFLSRGKRQEPPTPEGKLGRFPPMMHHHQAPSDGQT
PGARFQRSHLAEAFKAKGSGGGAGGGGSGRGLMGQIIPIYGFIFLYILYILFKVSRIILI
ILHQ

FIGURE 303

CGGCTCGAGTGCAGCTGTGGGGAGATTTCAAGTGCATTGCCTCCCCTGGGTGCTCTTCATCTT
GGATTTGAAAGTTGAGAGCAGCATGTTTTGCCCACTGAAACTCATCCTGCTGCCAGTGTTAC
TGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTCCATGTG
GGTGATTCACTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATATTCAAGAT
AGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATACTATTACTCCA
ATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGGTACACTTGATGGGGGACATCTTATGC
AATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGAACCTATATCTGTGA
AATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTACTGCATGTGCTTCCAG
AGGAGCCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAGATGGGATGTGTTTTCCAG
AGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTTTCAGGACGGCGCGCAAAGGA
GGAGATTGTATTTCTGTTACTACCACAACTCAGGATGTCTGTGGAGTACTCCCAGAGCTGGG
GCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATTTTCCGCAATGACGGTTCATCATG
CTTCAAGGAGTGAGGGAGTCAGATGGAGGAACTACACCTGCAGTATCCACCTAGGGAACCT
GGTGTTCAGAAAACCATTTGTGCTGCATGTGAGCCCGGAAGAGCCTCGAACACTGGTGACCC
CGGCAGCCCCTGAGGCCTCTGGTCTTGGGTGGTAATCAGTTGGTGATCATTGTGGGAATTGTC
TGTGCCACAATCCTGCTGCTCCCTGTTCTGATATTGATCGTGAAGAAGACCTGTGGAAATAA
GAGTTCAGTGAATTCTACAGTCTTGGTGAAGAACACGAAGAAGACTAATCCAGAGATAAAAG
AAAAACCCTGCCATTTTGAAAGATGTGAAGGGGAGAAACACATTTACTCCCCAATAATTGTA
CGGGAGGTGATCGAGGAAGAAGAACCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCA
CCCAGTTTGGCCTTCTCTGAGGTCAGATCGGAACAACTCACTTGAAAAAAGTCAGGTGGGG
GAATGCCAAAAACACAGCAAGCCTTTTTGAGAAGAATGGAGAGTCCCTTCATCTCAGCAGCGG
TGGAGACTCTCTCCTGTGTGTGTCCTGGGCCACTCTACCAGTGATTTCAGACTCCCGCTCTC
CCAGCTGTCTCCTGTCTCATTTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGG
CAGAGAGACTGGACAGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGC
CTCTGGAGTGGGACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCGTT
GGATCAGACCCCTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATA
AAAACCAACCCAAATCAA

FIGURE 304

MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLSPG
EHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTyceIRLKGES
QVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEIVFRYY
HKLMSVEYSQSWG HFQNRVNLVGDI FRNDGSIMLQGVRES DGGNYTCSIHLGNLVFKKTIV
LHVSPEEPRTLVT PAALRPLVLGGNQLV IIVGIVCATILLLPVLILIVKKTCGNKSSVNSTV
LVKNTKKTNPEIKEKPC HFERCEGEKHIYSPIIVREVIEEEEPSEKSEATYMTMHPVWPSLR
SDRNN SLEKKSGGGMPKTQQAF

FIGURE 305

CTATGAAGAAGCTTCCTGGAAAACAATAAGCAAAGGAAAACAAATGTGTCCCATCTCACATG
GTTCTACCCTACTAAAGACAGGAAGATCATAAACTGACAGATACTGAAATTGTAAGAGTTGG
AAACTACATTTTGCAAAGTCATTGAACTCTGAGCTCAGTTGCAGTACTCGGGAAGCCATGCA
GGATGAAGATGGATACATCACCTTAAATATTAAAACTCGGAAACCAGCTCTCGTCTCCGTTG
GCCCTGCATCCTCCTCCTGGTGGCGTGTGATGGCTTTGATTCTGCTGATCCTGTGCGTGGGG
ATGGTTGTGGGCTGGTGGCTCTGGGGATTTGGTCTGTGTCATGCAGCGCAATTACCTACAAGA
TGAGAATGAAAATCGCACAGGAACTCTGCAACAATTAGCAAAGCGCTTCTGTCAATATGTGG
TAAACAATCAGAACTAAAGGGCACTTTCAAAGGTCATAAATGCAGCCCCTGTGACACAAAC
TGGAGATATTATGGAGATAGCTGCTATGGGTTCTTCAGGCACAACTTAACATGGGAAGAGAG
TAAGCAGTACTGCACTGACATGAATGCTACTCTCCTGAAGATTGACAACCGGAACATTGTGG
AGTACATCAAAGCCAGGACTCATTTAATTCGTTGGGTCGGATTATCTCGCCAGAAGTCGAAT
GAGGTCTGGAAGTGGGAGGATGGCTCGGTTATCTCAGAAAATATGTTTGAGTTTTTGGAAGA
TGGAAAAGGAAATATGAATTGTGCTTATTTTCATAATGGGAAAATGCACCCTACCTTCTGTG
AGAACAAACATTATTTAATGTGTGAGAGGAAGGCTGGCATGACCAAGGTGGACCAACTACCT
TAATGCAAAGAGGTGGACAGGATAACACAGATAAGGGCTTTATTGTACAATAAAAGATATGT
ATGAATGCATCAGTAGCTGAAAAAAAAAAAAAA

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FIGURE 306

MQDEDGYITLNIKTRKPALVSVGPASSSWVRMALILLILCVGMVVGLVALGIWSVMQRNYL
QDENENRTGTLQQLAKRFCQYVVKQSELKGTFKGHKCSPCDTNWRYYGDSYGFRRHNLWE
ESKQYCTDMNATLLKIDNRNIVEYIKARTHLIRWVGLSRQKSNEVWKWEDGSVISENMFEBL
EDGKGNMNCAYFHNGKMHPTFCENKHYLMCERKAGMTKVDQLP

(30) 60/088,742	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,254	22 Jun/juin 1998 (22.06.1998)	US	(30) 60/091,478	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,810	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,355	23 Jun/juin 1998 (23.06.1998)	US	(30) 60/091,626	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,811	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,349	23 Jun/juin 1998 (23.06.1998)	US	(30) 60/091,628	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,824	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,429	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,633	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,825	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,431	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,646	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,826	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,435	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,673	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,858	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,444	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,978	7 Jul/juil 1998 (07.07.1998)	US
(30) 60/088,861	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,445	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,982	7 Jul/juil 1998 (07.07.1998)	US
(30) 60/088,863	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,461	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/092,182	9 Jul/juil 1998 (09.07.1998)	US
(30) 60/088,876	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,472	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/092,472	10 Jul/juil 1998 (10.07.1998)	US
(30) 60/089,090	12 Jun/juin 1998 (12.06.1998)	US	(30) 60/090,535	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/093,339	20 Jul/juil 1998 (20.07.1998)	US
(30) 60/089,105	12 Jun/juin 1998 (12.06.1998)	US	(30) 60/090,538	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/094,651	30 Jul/juil 1998 (30.07.1998)	US
(30) 60/089,440	16 Jun/juin 1998 (16.06.1998)	US	(30) 60/090,540	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/095,282	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,512	16 Jun/juin 1998 (16.06.1998)	US	(30) 60/090,557	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/095,285	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,514	16 Jun/juin 1998 (16.06.1998)	US	(30) 60/090,676	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,301	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,532	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,678	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,302	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,538	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,688	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,318	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,598	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,690	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,321	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,599	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,691	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,325	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,600	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,694	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,916	10 Aug/août 1998 (10.08.1998)	US
(30) 60/089,653	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,695	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,929	10 Aug/août 1998 (10.08.1998)	US
(30) 60/089,801	18 Jun/juin 1998 (18.06.1998)	US	(30) 60/090,696	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/096,012	10 Aug/août 1998 (10.08.1998)	US
(30) 60/089,907	18 Jun/juin 1998 (18.06.1998)	US	(30) 60/090,862	26 Jun/juin 1998 (26.06.1998)	US	(30) 60/096,143	11 Aug/août 1998 (11.08.1998)	US
(30) 60/089,908	18 Jun/juin 1998 (18.06.1998)	US	(30) 60/090,863	26 Jun/juin 1998 (26.06.1998)	US	(30) 60/096,146	11 Aug/août 1998 (11.08.1998)	US
(30) 60/089,947	19 Jun/juin 1998 (19.06.1998)	US	(30) 60/091,358	1 Jul/juil 1998 (01.07.1998)	US	(30) 60/096,757	17 Aug/août 1998 (17.08.1998)	US
(30) 60/089,948	19 Jun/juin 1998 (19.06.1998)	US	(30) 60/091,360	1 Jul/juil 1998 (01.07.1998)	US	(30) 60/096,766	17 Aug/août 1998 (17.08.1998)	US
(30) 60/089,952	19 Jun/juin 1998 (19.06.1998)	US	(30) 60/091,544	1 Jul/juil 1998 (01.07.1998)	US	(30) 60/096,768	17 Aug/août 1998 (17.08.1998)	US
(30) 60/090,246	22 Jun/juin 1998 (22.06.1998)	US	(30) 60/091,486	2 Jul/juil 1998 (02.07.1998)	US	(30) 60/096,773	17 Aug/août 1998 (17.08.1998)	US
(30) 60/090,252	22 Jun/juin 1998 (22.06.1998)	US	(30) 60/091,519	2 Jul/juil 1998 (02.07.1998)	US	(30) 60/096,791	17 Aug/août 1998 (17.08.1998)	US

(30) 60/096,867	17 Aug/aout 1998 (17.08.1998)	US
(30) 60/096,891	17 Aug/aout 1998 (17.08.1998)	US
(30) 60/096,894	17 Aug/aout 1998 (17.08.1998)	US
(30) 60/096,895	17 Aug/aout 1998 (17.08.1998)	US
(30) 60/096,897	17 Aug/aout 1998 (17.08.1998)	US
(30) 60/096,949	18 Aug/aout 1998 (18.08.1998)	US
(30) 60/096,950	18 Aug/aout 1998 (18.08.1998)	US
(30) 60/096,959	18 Aug/aout 1998 (18.08.1998)	US
(30) 60/096,960	18 Aug/aout 1998 (18.08.1998)	US
(30) 60/097,022	18 Aug/aout 1998 (18.08.1998)	US
(30) 60/097,141	19 Aug/aout 1998 (19.08.1998)	US
(30) 60/097,218	20 Aug/aout 1998 (20.08.1998)	US
(30) 60/097,661	24 Aug/aout 1998 (24.08.1998)	US
(30) 60/097,951	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,952	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,954	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,955	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,971	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,974	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,978	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,979	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/097,986	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/098,014	26 Aug/aout 1998 (26.08.1998)	US
(30) 60/098,525	31 Aug/aout 1998 (31.08.1998)	US
(30) 60/100,634	16 Sep/sep 1998 (16.09.1998)	US
(30) 60/115,565	12 Jan/jan 1999 (12.01.1999)	US